

British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008

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Introduction

The success of antenatal testing for HIV means that more clinicians than ever are involved in the care of women with HIV who are pregnant. Despite very few recent randomized controlled trials regarding the use of antiretroviral therapy (ART) in pregnancy or obstetric interventions, practice is changing. This is informed largely by observational data and

theoretical considerations and these guidelines reflect this. The Cochrane Systematic Review of randomized controlled trials in this area shows how limited the guidelines would be were they to be restricted to such high-level evidence.

Changes from the 2005 guidelines include the following.

- A greater range of clinical scenarios to include more consideration of adverse obstetric events, especially prematurity. This reflects the nature and volume of calls to the Writing Committee from fellow clinicians.
- Clearer recommendations regarding documentation of antenatal HIV testing, consideration to be given to repeat testing of women noted to be at continuing higher risk of HIV acquisition and advice to recommend near-patient HIV testing for untested women in labour.
- A further reduction in detail on teratogenicity, as this is better covered by reference to the Antiretroviral Pregnancy Registry.
- There are few substantive changes to the recommendations on the use of individual antiretroviral therapies. The option of zidovudine monotherapy plus pre-labour Caesarean section (PLCS) for selected women is supported by new data from the UK and Ireland cohort.
- There is more detail in the obstetric management section, reflecting the greater diversity of clinical situations being encountered, in part as a result of more women choosing to take short-term antiretroviral therapy (START) and try for an elective vaginal delivery. Data from two large European cohorts provide support for planning a vaginal delivery if HIV virus is undetectable on highly active antiretroviral therapy (HAART).
- The recommendations for infant feeding in the UK remain unchanged.

1.0 Summary of recommendations

1.1 Section 4. Antenatal HIV testing (Recommendation Grade C/Level IV)

1.1.1 *Maintaining and improving antenatal test uptake*

- All pregnant women should be recommended HIV testing at an early stage in pregnancy, or as soon as possible if they present for antenatal care at a later stage.
- Simple, robust and uniform systems are needed in all units and areas to record the number of women booking for antenatal care, being offered an HIV test, declining or accepting the offer and being tested.

1.1.2 *Identifying seroconversions in pregnancy*

- The number of infected infants born to women who test negative in early pregnancy is low. Nevertheless, any

indication that a woman is at continuing risk of acquiring infection in pregnancy should be recorded, and repeat testing offered.

1.1.3 Rapid testing

- Rapid or near-patient testing should be considered for women who arrive in labour unbooked and a reactive result should be acted upon.

1.1.4 Recording HIV test results

- Midwives and doctors reviewing women during antenatal care should ensure that the HIV test result is clearly documented.
- Staff undertaking invasive genetic screening tests must be aware of a woman's HIV status.
- Labour ward staff must be aware of a woman's HIV status. Test results should be available on labour wards, with clear protocols for checking the status of women arriving in labour.

1.2 Section 5. Preconception and fertility management in men and women infected with HIV (Recommendation Grade B/Level III)

- Self-insemination of partner's semen is recommended to protect the uninfected male partner of an HIV-positive female and is easily performed by the couple.
- Fertility assessment is indicated if conception has not occurred after 6–12 months of self-insemination.
- Sperm-washing is recommended to protect the uninfected female partner of an HIV-positive male, but is expensive, currently only provided by a few centres and patient-funded in over 50% of cases.

1.3 Section 6. Sexual health of HIV-positive pregnant women (Recommendation Grade C/Level IV)

- Routinely screen for genitourinary tract infections at presentation.
- Consider re-screening in the third trimester.
- Repeat treponemal serology in the third trimester.

1.4 Section 7. Psycho-social issues (Recommendation Grade C/Level IV)

- The minimum composition of the antenatal multi-disciplinary team (MDT) is: HIV specialist, obstetrician, specialist midwife and paediatrician.
- A thorough early assessment of the social circumstances of a newly diagnosed HIV-positive pregnant woman is essential.

- HIV-positive pregnant women should be encouraged to disclose their HIV status to their partner.
- Testing any other children for HIV is recommended.

1.5 Section 8. Viral load and resistance (Recommendation Grade C/Level IV)

- Viral load is an important determinant of transmission.
- Quantify HIV plasma load:
 - at least every 3 months and at week 36 in women on established therapy;
 - 2 weeks after starting or changing therapy;
 - at delivery.
- Use a second assay where there are discrepancies among viral load, CD4 cell count and clinical status.
- Determine HIV genotype (or phenotype):
 - pre-therapy (at presentation);
 - if viraemic on established therapy;
 - at delivery if on monotherapy;
 - within 6 weeks of stopping suppressive therapy.

1.6 Section 9. Management of opportunistic infections in pregnancy (Recommendation Grade C/Level IV)

- Investigations and management should not be delayed because of pregnancy.
- Management of opportunistic infections is rarely altered by pregnancy.

1.7 Section 10. Antiretroviral therapy in pregnancy: efficacy (Recommendation Grades A–C/Levels I–IV; see individual scenarios)

- See individual scenarios.
- Balance the risk of HIV transmission with the toxicities of therapy.
- Zidovudine (ZDV) monotherapy, which should be commenced by 28 weeks, remains a valid option for women:
 - with repeatedly $<6\text{--}10\,000$ HIV RNA copies/mL plasma;
 - with wild-type virus;
 - not requiring HAART for maternal health;
 - not wishing to take HAART during pregnancy;
 - willing to deliver by PLCS.
- Do not prescribe dual nucleoside reverse transcriptase inhibitor (NRTI) therapy.
- Prescribe effective (≥ 3 drug) combination therapy:
 - if indicated for maternal health as per adult guidelines, starting after the first trimester;

- if baseline maternal viraemia >10 000 copies/mL and no maternal indication for HAART, commencing at 20–28 weeks;
- as an alternative to ZDV monotherapy plus PLCS;
- if drug resistance detected on genotype/phenotype.
- Short-term antiretroviral therapy (START) for prevention of mother-to-child transmission should:
 - be discontinued after delivery, ideally when viral load <50 copies/mL;
 - be discontinued with careful consideration of the half-life of each component to avoid unplanned monotherapy after stopping, especially for drugs with a low genetic barrier to resistance.
- Avoid stavudine plus didanosine as the NRTI backbone whenever possible (and monitor lactate if unavoidable).
- HAART commenced prior to conception should usually be continued throughout pregnancy.

1.8 Section 11. Antiretroviral therapy in pregnancy: toxicity (Recommendation Grade B/Level III)

- The association between protease inhibitors (PIs) and impaired glucose tolerance is inconclusive.
- HAART is associated with pre-term delivery (PTD), especially delivery before 34 weeks.

1.9 Section 12. Antiretroviral therapy and pregnancy: pharmacokinetics (Recommendation Grade C/Level IV)

- Use current adult doses for all ART in pregnancy.
- Use therapeutic drug monitoring of PIs and new agents where available.

1.10 Section 13. Obstetric management of pregnancy and delivery (Recommendation Grades A–C/Levels Ib–IV; see individual scenarios)

- In addition to any obstetric considerations, PLCS is recommended for:
 - all women taking ZDV monotherapy;
 - women on combination therapy with detectable (>50 copies/mL) viraemia.
- PLCS should be considered for women with HIV/hepatitis C virus (HCV) coinfection.
- PLCS is an option for women with undetectable plasma HIV on HAART.
- PLCS to prevent mother-to-child transmission should be planned for:

- 38 weeks for women who have detectable (>50 copies/mL) viraemia or who are on ZDV monotherapy;
- 39 weeks for women who have undetectable viraemia and who are on HAART.

- Elective vaginal delivery is an option for women with no detectable viraemia on HAART.
- Avoid invasive monitoring of foetus and artificial rupture of membranes.
- Prescribe appropriate peri-operative antibiotics for all Caesarean sections and for pre-labour rupture of membranes.
- Give corticosteroids for threatened pre-term delivery <34 weeks.
- Consider maternal single-dose nevirapine (NVP) in threatened pre-term delivery to load the baby who may not be able to take oral medication.
- Consider expedited delivery for pre-term pre-labour rupture of membranes (PPROM).
- Expedited delivery for term pre-labour rupture of membranes (PROM).
- Communication between team members is essential and each delivery (by whatever mode) should be planned.
- Ensure provision of appropriate formulations of neonatal therapy on the delivery/postnatal ward.
- Give the mother a written care plan with contact details for emergency admissions.
- Advise ART for invasive genetic diagnostic tests.
- Intravenous ZDV is indicated for mothers on ZDV monotherapy and for mothers with >50 HIV RNA copies/mL plasma on HAART.

1.11 Section 14. Pregnancy and HIV-2 infection (Recommendation Grade C/Level IV)

- Ensure that HIV-2 infection is diagnosed.
- If HIV-2 viral load is known to be <50 copies/mL antenatal/peripartum, neonatal intervention may be unnecessary.
- If HIV-2 is detectable, appropriate (HIV-2-specific) HAART is recommended.
- Do not prescribe nonnucleoside reverse transcriptase inhibitors (NNRTIs) or ZDV monotherapy.
- Breastfeeding is probably best avoided.
- Vaginal delivery is an option if HIV-2 viral load is undetectable.

1.12 Section 15. HIV and hepatitis B and C coinfections (Recommendation Grade C/Level IV)

- All HIV-positive pregnant women should be tested for hepatitis B virus (HBV).

- Infants born to women who are HBV surface antigen (HBsAg) positive and HBV envelope antigen (HBeAg) positive, as well as those with high levels of HBV viraemia, should receive HBV vaccination with additional passive immunization with HBV immunoglobulin (HBIG).
- ART for pregnant women with HIV/HBV coinfection should include drugs with activity against HBV.
- All HIV-positive pregnant women should be tested for HCV.
- HCV-positive HIV-positive women should be treated with combination ART.
- PLCS should be considered for all mothers coinfecting with HIV and HCV.

1.13 Section 16. Management of infants born to HIV-infected mothers (Recommendation Grades A–C / Levels Ib–IV)

- Most infants should be given ZDV monotherapy twice daily (bid) for 4 weeks.
- Alternative suitable ART monotherapy may be given if maternal therapy does not include ZDV.
- Triple therapy should be given as post-exposure prophylaxis (PEP) for infants born to untreated mothers or mothers with detectable viraemia despite combination therapy.

1.13.1 Safety

- There is no evidence of any increase in congenital malformations in humans with first trimester exposure to any ART (including efavirenz) to date.
- There are inadequate data to exclude a teratogenic risk for most individual drugs and for all combinations.
- There is laboratory evidence of mitochondrial depletion in infants exposed to ART perinatally but the clinical importance of this is uncertain.
- Prolonged haematological (but not clinical) effects of ZDV have been reported in exposed uninfected infants.

1.13.2 Laboratory diagnosis of HIV infection in nonbreastfed infants

- To exclude HIV infection, DNA polymerase chain reaction (PCR) is required on at least two occasions off therapy.
- Primers known to amplify maternal virus should be used.
- Triple therapy in neonates can delay diagnosis of infection.
- Document loss of maternal antibody at 18 months.

1.14 Section 17. Infant feeding (Recommendation Grade B/Level IIb)

- Recommend exclusive formula-feeding to all HIV-positive mothers.

2.0 Scenarios: interventions to reduce mother-to child transmission of HIV

Table A1 summarizes nine clinical scenarios, where a different approach to therapy in pregnancy may need to be considered. The issues relating to each scenario are discussed in this section as well as in other sections of the text. The classification of levels of evidence and grades of recommendations are summarized in Table 6.

See clinical scenarios and Section 16 on paediatric management for information regarding ART for the neonates as well as Tables 4 and 5. As a general principle, when interventions go according to plan and there is no relevant resistance, a monotherapy component of the maternal regimen, usually ZDV, is administered to the baby for 4 weeks. Where the baby is about to be delivered and the viral load is not fully suppressed, unless the plan was for the mother to have ZDV monotherapy and a PLCS, the baby is likely to need combination PEP, which, if there is no contraindication, will usually consist of ZDV, lamivudine (3TC) and NVP.

2.1 Scenario 1: where mothers do not yet require treatment for their HIV infection

Asymptomatic women who do not require antiretroviral treatment for their own health, according to current British HIV Association (BHIVA) guidelines, may be treated with START commencing in the second trimester with standard HAART regimens with the intention to achieve undetectable viral loads of <50 copies/mL prior to delivery. At present it is recommended that this should contain ZDV and 3TC unless there are any contraindications. It is also recommended that this regimen should contain a boosted PI. PIs have a greater barrier to resistance development than NNRTIs and can be stopped concurrently with the NNRTI backbone. In addition, PI pill burden and tolerance are improving with newer formulations and there is a low incidence of severe short-term side effects. If NNRTIs are used, these must be discontinued carefully in a planned manner to cover the NNRTI 'tail' and avoid the development of maternal drug resistance. The optimal time to commence START is unclear but the aim should be to start by 28 weeks. Commencing prior to foetal viability (24 weeks) may be prudent. An earlier start between 20 and 24 weeks may be advisable for a woman with a high

baseline viral load who is aiming to achieve an undetectable viral load by 36 weeks in order to proceed to a vaginal delivery. If the viral load is < 50 copies/mL at 36 weeks, a trial of labour can be anticipated. Intravenous ZDV is not considered necessary in this situation and oral dosing of HAART should continue throughout delivery. Some mothers who achieve an undetectable viral load will still prefer a PLCS, which should be scheduled for 39 weeks (see Section 13).

An alternative approach, in women who do not require treatment for themselves, and who repeatedly have a viral load of < 10 000 copies/mL, is to use ZDV monotherapy, combined with a PLCS at 38 weeks, with a ZDV infusion commencing 4 h prior to the section. The risk of vertical transmission is low, and this reduces antiretroviral exposure of the foetus in pregnancy. The risk of pre-term delivery is significantly lower with this approach than with the use of HAART. In addition, maternal toxicity is reduced and the risk of the development of resistance in the mother, when used at this level of viral load, appears minimal.

The optimal time to commence ZDV monotherapy is unclear but ideally this should be commenced by 28 weeks, and commencing prior to foetal viability (24 weeks) may be prudent.

2.2 Scenario 2: mother needs to start HAART for her own health

Women who are deemed to need HAART for their own health should commence HAART early, although it can usually be deferred until after the first trimester. It is recommended that these women should be treated with antiretroviral regimens as per the BHIVA Guidelines for The Treatment of HIV Infected Adults with Antiretroviral therapy (2006; www.bhiva.org/cms1191541.asp).

Consideration should be given to safety and efficacy data available in pregnancy, tolerability and whether treatment is likely to be continued after delivery. There is most experience in pregnancy with ZDV and 3TC as the NRTI backbone, which is therefore usually recommended in combination with either a PI or an NNRTI drug (see Section 5). If an undetectable viral load is achieved by 36 weeks a trial of labour may be possible as in Scenario 1. If the viral load is > 50 copies/mL at 36 weeks, see Scenario 4.

2.3 Scenario 3: mother conceives on HAART

If a mother conceives on HAART, has an undetectable viral load, and is tolerating the combination well she should have the pros and cons of continuing this regimen discussed. As a general principle, however, in this situation she should be encouraged to continue this regimen, even if

it contains efavirenz. The antiretroviral pregnancy register does not show an additional risk with this approach (www.apregistry.com) (see Section 11). Obstetric management should be as per Scenario 2 with the option of a trial of labour or a PLCS at 39 weeks depending on maternal wishes or obstetric history.

If the mother conceives on HAART, which is failing, then this should be changed appropriately to ensure the lowest possible viral load at the time of delivery. Resistance testing can help to identify the best options. If the viral load is < 50 copies/mL at 36 weeks than she can proceed as above; if not, see Scenario 4.

2.4 Scenario 4: On START or HAART with viral load > 50 copies/mL at 36 weeks

A genotype test should be performed and treatment changed to the best option. A PLCS should be planned for 38 weeks with 4 h of intravenous ZDV if the genotype does not show resistance to ZDV. Combination PEP should be prescribed to the neonate based on the genotype. Consider the use of single-dose NVP given to the mother, to load up the baby.

2.5 Scenario 5: Late presentation > 32 weeks, before onset of labour

With improved turnaround times for viral load testing, a woman presenting beyond 32 weeks may still be managed with a view to a possible vaginal delivery if she commences HAART and achieves a viral load of < 50 copies/mL by 36 weeks as in Scenario 2. If the viral load is > 50 copies/mL at 36 weeks she should have a PLCS at 38 weeks with intravenous ZDV, and the baby should receive combination PEP.

2.6 Scenario 6: threatened pre-term delivery + / - rupture of membranes

A vaginal swab should be taken for bacteriology, and if gestation < 34/40, intramuscular steroids should be started, aiming for two doses 24 h apart for foetal lung maturation. If the mother is drug naïve, take baseline bloods for CD4 cell count and viral load if not known, and commence HAART. NVP should be included in the regimen as it crosses the placenta rapidly. This can be in the form of single-dose NVP commenced at the same time as PI-based HAART if the CD4 cell count is high or unknown, or an ongoing NVP-containing regimen if the CD4 cell count is low. If ongoing NVP is commenced without knowledge of the CD4 cell count, ensure that the baseline CD4 result is

checked with a plan to substitute the NVP if the CD4 cell count is high.

If the mother is already on HAART but the viral load is >50 copies/mL, review and optimize HAART and add single-dose NVP for the reasons given above. For the mother on HAART with a viral load <50 copies/mL, continue HAART, but consider single-dose NVP, especially if <32 weeks, if she is not on an NNRTI.

Once two doses of steroids have been administered, the decision of whether to perform an emergency Caesarean section at <34 weeks can be taken. The timing of this procedure will involve balancing the risk of mother-to-child transmission of HIV-1 with the risks of severe prematurity ($<30/40$). This should involve multidisciplinary discussion with the obstetricians, neonatologists and HIV physicians. The decision to deliver will balance HIV transmission risk with foetal age and size and neonatal facilities. At >30 weeks this balance may favour proceeding to an emergency Caesarean section once two doses of steroids have been administered, and ≥ 34 weeks an emergency Caesarean section should be performed as soon as possible. There have been no randomized controlled trials to inform these decisions.

In the scenario of threatened pre-term labour, or PPRM in a patient either not yet on HAART or with a known viral load >50 copies/mL as well as the measures above, it may be worth commencing intravenous ZDV. This can be reviewed taking into consideration which drugs have been commenced, what the viral load is, and the likely timescale of delivery.

2.7 Scenario 7: term pre-labour rupture of membranes

The antiretroviral management in this situation is as for Scenario 6. Commence HAART, including a single dose of NVP and intravenous zidovudine, and proceed to Caesarean section after 2–4 h. If the mother is on HAART with a fully suppressed viral load, a decision should be made as to whether induction of labour, as opposed to an emergency Caesarean section, is possible.

2.8 Scenario 8: mother diagnosed after delivery

Where it is only ascertained after delivery that an infant has been born to an HIV-infected mother, where maternal interventions have been declined or when interventions were introduced after labour had started, PEP should be offered as soon as possible. There are observational data indicating that ZDV can reduce transmission in this situation if given within 48 h of delivery. It would seem logical, and consistent with other PEP regimen recommen-

dations for high-risk exposure, to offer triple-combination therapy for 4 weeks, although there are no data on this.

2.9 Scenario 9: mother presents in labour

If the mother's HIV status is unknown, a point of care test should be performed where possible and a reactive result must be acted on immediately. If the result is reactive or she is known to be HIV positive, baseline samples should be taken and NVP-containing HAART commenced (either as single-dose NVP with a PI-containing regimen, or as an ongoing NVP regimen; see Scenario 6). Intravenous ZDV should also be commenced. If the mother is not about to deliver, an emergency Caesarean section should be performed at least 2 h post NVP.

NB: In any of the above scenarios when NNRTI-containing HAART is administered to the mother, with a view to discontinuing HAART following delivery, therapy should be discontinued in a manner designed to avoid inadvertent NNRTI monotherapy.

3.0 Background: UK prevalence of HIV in pregnancy and risk of transmission

The prevalence of HIV infection amongst women giving birth in the UK has increased every year since 1990. Results from the unlinked anonymous survey based on residual neonatal dried blood spots show that in 2006 the prevalence of HIV infection in women giving birth reached 1 in 238 (0.42%) in London, 1 in 705 (0.14%) in the rest of England, and 1 in 440 (0.23%) in England and Scotland overall [1]. The majority of these women were from sub-Saharan Africa. In 2006, 1100 children were born in the UK to women diagnosed with HIV infection [2].

In the UK, the rate of mother-to-child transmission from diagnosed women was 25.6% in 1993, at which time interventions were virtually nonexistent [3], whereas between 2000 and 2006, with high uptake of interventions, the transmission rate was 1.2% [95% confidence interval (CI) 0.9–1.5%]. Transmission rates were not significantly different according to whether mothers were on HAART, regardless of mode of delivery (PLCS *vs.* planned vaginal delivery), or taking ZDV monotherapy and delivering by pre-labour Caesarean section [4].

In untreated women the risk of transmission is related to maternal health, obstetric factors and infant prematurity. Overall there is a close linear correlation between maternal viral load and risk of transmission, but rare transmissions have been reported even when plasma viraemia was <400 HIV RNA copies/mL [5]. The only obstetric factors that consistently show an association with risk of transmission

are mode of delivery, duration of membrane rupture and delivery before 32 weeks of gestation.

4.0 Antenatal HIV testing

Prior to the widespread implementation of the routine offer and recommendation of antenatal HIV testing in the UK, detection rates prior to delivery were poor. In the mid-1990s only about one-third of infected pregnant women were diagnosed, and most of those were aware of their infection status before they became pregnant [6]. In England, the routine offer policy was laid out in a Health Service Circular issued in 1999; this proposed a 90% uptake target by the end of 2002, with the aim of diagnosing 80% of infected women before delivery in time to offer appropriate interventions [7]. Similar policies were subsequently adopted elsewhere in the UK and had already been put in place in the Republic of Ireland.

By the end of 2003 virtually all UK maternity units had implemented the routine offer policy [8]. While over two-thirds achieved >80% uptake in 2003 only about one-third reached the 90% target. More recent national data are not available, but standards for monitoring antenatal HIV screening were published in 2003 [9], and routine national and regional audit systems are currently being developed.

Despite the improved uptake, as the prevalence of HIV in pregnancy continues to rise, a substantial number of women remain undiagnosed by the time of delivery, leading to potentially avoidable cases of mother-to-child transmission.

Between 2000 and 2004 the majority of HIV-infected women diagnosed before delivery were identified through antenatal testing. However, since 2005 the situation has reversed and a greater proportion of infected women are already diagnosed before they conceive [2]. An audit of the circumstances surrounding nearly 90 perinatal transmissions in England in 2002–2005 demonstrated that over two-thirds of these infants were born to women who had not been diagnosed prior to delivery. About half of those undiagnosed women had declined antenatal testing. A smaller proportion had tested negative and were likely seroconversions in pregnancy. At present, although desirable, there is no suggestion that universal retesting in the third trimester will become national policy and therefore case-by-case assessment to determine whether a woman is at continuing risk of acquiring HIV infection in pregnancy is the only option with repeat testing offered. Many of the recommendations of this audit are incorporated in the relevant sections of these guidelines (www.esussexiaiu.nhs.uk/docs/specialised/VerticaltransmissionFullreportOctober2007.pdf).

Rapid or near-patient testing should be recommended to women who arrive in labour unbooked and a reactive result should be acted on immediately (see Scenario 9).

5.0 Preconception and fertility management in men and women infected with HIV

5.1 Preconceptual advice

1. Aim to delay conception until opportunistic infections have been treated and *Pneumocystis carinii* pneumonia (PCP) prophylaxis is no longer required (Section 9).
2. Commence folic acid.
3. Discuss switching away from didanosine and efavirenz if reasonable alternatives are available and viral suppression is not likely to be jeopardized (Section 11).
4. Avoid transmission to partner, especially if uninfected.

There are three aspects to consider: interventions that can minimize the risk of transmission between discordant couples during conception, the management of any fertility issues, and the state of health and medication of the infected partner preconceptually.

In discordant couples in which the male partner is infected with HIV, assisted conception with either sperm washing or donor insemination is significantly safer than timed unprotected intercourse and should be advised in all cases. In these couples, presuming a stable relationship, HIV transmission risk per act of unprotected intercourse is reported to be between 0.03 and 0.001% [10,11]. The risk is significantly reduced if the male partner has undetectable viral load through use of HAART but is not eliminated as significant virus can still be shed in semen under these conditions, as serum and semen viral load are not always correlated [12,13]. The risk can be further reduced by limiting exposure to the fertile period of the female cycle and ensuring that all genital tract infections have been treated. The only prospective study of couples trying to conceive through timed intercourse was conducted before the routine use of HAART, and 4% of the female partners seroconverted [14]. A more recent retrospective study in Spain of 40 discordant couples conceiving, in which the male partner had fully suppressed HIV replication on therapy for at least 6 months, reported no transmissions [15]. Numbers are too small to allow any valid conclusions to be drawn about the safety of natural conception in such cases, but the study reflects common practice. Further prospective studies are warranted. Alternative options for serodiscordant couples, well established to reduce risk, include donor insemination, which removes the possibility of genetic parenthood from the infected male but

eliminates any risk of HIV transmission during conception, and sperm washing. Sperm washing is a procedure during which live sperm, which do not carry HIV, are separated from HIV-contaminated seminal plasma and nongerminal cells by centrifugation before being used in an insemination or *in vitro* fertilization (IVF) procedure [16]. The efficacy of the wash is then verified with a post-wash HIV RNA assay before the sperm are used in treatment [17]. The treatment is relatively simple and significantly safer than timed unprotected intercourse, with no cases of seroconversion in either female partner or child born in over 3000 cycles of sperm washing combined with intrauterine insemination, IVF or intra-cytoplasmic sperm injection (ICSI) reported in the literature to date [18,19]. To minimize the risks of multiple pregnancy and ovarian hyperstimulation, couples should have natural cycle insemination unless fertility factors are identified, when fertility drugs for superovulation or IVF/ICSI should be considered. The disadvantage of sperm washing is that the treatment is at present only provided by a limited number of fertility centres in the UK, Europe and Northern America. National Institute of Clinical Excellence guidelines published in February 2004 on fertility have recommended sperm washing in serodiscordant couples as a risk-reduction process [20]. This has led to a significant increase in the number of Primary Care Trusts willing to fund up to three cycles of sperm-washing treatment on the basis of risk reduction (C. Gilling-Smith, personal communication). A letter of recommendation from the genitourinary physician to the patient's Health Authority is usually required. Couples should be provided with information and counselling on donor insemination and sperm washing, including advice on how to access such treatment to allow them to make an informed choice.

The risk of viral transmission for discordant couples in which the female partner is infected with HIV is reduced but not eliminated when the viral load is undetectable through HAART. The current recommendation is that these couples should avoid unprotected intercourse and be advised on the technique of self-insemination during the fertile time of the cycle using quills, syringes and sterile containers [18]. Fertility investigations should be initiated when pregnancy is not achieved after 6–12 months of self-insemination, or sooner in women over 35 years or those with irregular cycles or a history suggestive of tubal disease [18,21]. While the issue of superinfection in concordant couples continues to be debated [22,23], current recommendations for these couples are to avoid unprotected intercourse and to consider sperm washing to minimize the risk of transmitting a viral variant to the female partner and future child. If the couple are not able to access or afford such services then they should be fully counselled on the risks of superinfection.

It is now well accepted that HIV-infected men and women should not be denied access to fertility treatment, provided that the welfare of the child has been addressed [24–27]. The Human Fertilisation and Embryology Authority (HFEA) Act (1990) requires treatment centres to take into account the state of health of both prospective parents and social circumstances in respect of the welfare of any child arising as a result of treatment. Consideration should be given to maternal prognosis (treatment options and adherence) and commitment to comply with interventions during pregnancy and postnatally to minimize vertical transmission risk.

Assisted reproductive techniques for infertility such as IVF should continue to be monitored, as little is known of the impact of invasive procedures such as intrauterine insemination, oocyte retrieval and embryo transfer on the risk of vertical transmission [21]. Centres electing to treat HIV-infected patients should have separate laboratory facilities to eliminate the risk of cross-contamination to uninfected samples [21].

In the UK, sperm-washing is currently available at the Chelsea and Westminster Hospital (www.londonfertility.co.uk).

6.0 Sexual health of HIV-positive pregnant women

There are few data regarding the prevalence of genital infections in HIV-positive women in the UK [28]. At present, the majority of pregnant HIV-infected women in the UK come from, and mostly acquired HIV in, sub-Saharan Africa where the prevalence of genital infections, particularly in the HIV-infected population, can be high [29]. Recent figures from the Health Protection Agency show that, while the prevalence of HIV infection among pregnant women born in sub-Saharan Africa has remained relatively stable in recent years (2.2% in 2000 and 2.4% in 2006), there has been a threefold increase in prevalence among women born in Central America and the Caribbean over the same period, rising from 0.21% in 2000 to 0.61% in 2006 [1]. A high prevalence of genital infections in women of Afro-Caribbean origin has been reported [30]. The diagnosis and treatment of genital infections in any individual have clear benefits, in terms of both individual morbidity and possible infectivity to any sexual partner. In pregnancy, the welfare of the baby is an additional issue. However, apart from the recommendation that all pregnant women should be screened for HIV, HBV and syphilis, asymptomatic pregnant women in the UK are not routinely screened for genital infections.

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth [31,32].

Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with mother-to-child transmission of HIV and may be interlinked [33–35]. However, a phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission showed no benefit in reducing mother-to-child transmission in the context of single-dose NVP prophylaxis. Although both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been associated with chorioamnionitis, the organisms usually implicated are those associated with bacterial vaginosis (BV) and *Ureaplasma urealyticum* [31,32]. A strong association between BV and premature delivery has been reported [32,36]. There are data from Malawi that suggest that BV may be associated with an increased risk of maternal HIV infection in pregnancy as well as premature delivery and mother-to-child transmission of HIV [37]. Further work is needed. A large meta-analysis assessing the effects of antibiotic treatment of BV in pregnancy does not support the routine screening for and treatment of BV in pregnant HIV-negative women [38,39]. However, the available evidence cannot rule out a small benefit in pregnancy outcome associated with the screening and treatment of BV. As the numbers of HIV-1 infected women are relatively small and the risk of screening and treating for BV is small, and given the potential for increased mother-to-child transmission of HIV-1 in the presence of BV and the fact that HIV-positive pregnant women are recommended to undergo sexually transmitted disease (STD) screening, it seems reasonable to screen and treat for BV in this high-risk group.

It has long been recognized that genital infections, in particular ulcerative diseases, are associated with sexual transmission of HIV [40,41]. This may be a consequence of an increase in local HIV replication resulting in a higher viral load in genital secretions, secondary to the presence of specific organisms, and/or ulceration and inflammation [42,43]. A study from Zimbabwe has shown a correlation between herpes simplex virus type 2 (HSV-2) antibody status and HIV-1 mother-to-child transmission [44]. A study from Thailand showed that perinatal cervicovaginal lavages (CVL) HSV-2 shedding was associated with increased risk of intrapartum HIV transmission and that the effect was independent of CVL and plasma HIV viral load. This study was, however, carried out in the context of either ZDV monotherapy from 36 weeks or placebo [45]. That there may still be an increased risk associated with HSV shedding with patients on HAART is suggested by a randomized, double-blind, placebo-controlled trial of herpes-suppressive therapy in HIV-1/HSV-2-infected women taking HAART in Burkina Faso, which demonstrated that valacyclovir 500 mg twice a day further reduced genital HIV replication in those women with

residual HIV shedding despite ART [46]. Genital HSV should be treated as per nonpregnant women. Continuous suppressive therapy with acyclovir may be required, and is effective and safe [47].

Organisms associated with BV have been shown to stimulate HIV expression *in vitro* [48,49]. A study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis [50]. Viral load in cervicovaginal specimens has been shown to correlate with mother-to-child transmission of HIV-1 [51]. Genital tract viral load will usually mirror the plasma viral load [52], but there is increasing evidence of compartmentalization of HIV-1 between the plasma and genital tract. Genital tract HIV-1 has been detected in women with an undetectable plasma viral load [53,54] and genetic diversity of virus from the two compartments has been reported [55]. A number of factors may be responsible for this, including differential drug penetration into body compartments and the presence of genital tract infections. At present the majority of HIV-infected pregnant women in the UK deliver by PLCS but, increasingly, those women with an undetectable plasma viral load are undergoing a trial of labour. In addition, women planning a PLCS may rupture their membranes prematurely which may result in a vaginal delivery. Thus, an increasing number of foetuses will be exposed to the cervicovaginal secretions of HIV-positive women.

In the absence of randomized controlled trials, but for the reasons outlined above, it would continue to appear prudent to screen HIV-positive pregnant women for genital infections. This should be done as early as possible in pregnancy and consideration should be given to repeating this at around 28 weeks. Syphilis serology should be performed on both occasions. In addition, any infection detected should be treated according to the UK national guidelines, followed by a test of cure. Partner notification should take place where indicated, to avoid re-infection.

In pregnancy, warts are often more severe and less responsive to therapy, which may need to be deferred to the postpartum period. Cytology should be undertaken in pregnancy as for HIV-seronegative women. If an abnormality is detected referral should be made for colposcopy, which can be undertaken irrespective of gestation. If cervical intraepithelial neoplasia (CIN) is seen at colposcopy, it is customary to repeat the colposcopy on one or two occasions during the pregnancy to ensure that there are no signs of invasive cancer developing. Usually, if any abnormality is detected, treatment is deferred until 6 weeks after delivery, unless invasive cervical cancer is suspected, when biopsies will be required. Irrespective of

HIV status, it is prudent to perform these in the operating theatre, as bleeding may be brisk.

7.0 Psychosocial issues

HIV diagnosis during pregnancy may be a profoundly shocking and life-changing experience for the newly diagnosed HIV-positive woman. There may be a complex mix of emotional, psychosocial, relationship, economic and even legal issues that arise directly out of the HIV diagnosis. The newly diagnosed woman also has a relatively brief time in which she needs to be able to develop trust in her medical carers and attain sufficient medical knowledge of her situation to be able to make appropriate informed decisions that will affect the long-term health of herself, her foetus and her male partner.

The prevention of mother-to-child transmission can only be achieved if the pregnant woman embraces the medical interventions appropriately. In a number of cases the psychosocial issues may threaten to impede or obstruct the process of reducing mother-to-child transmission.

7.1 The antenatal HIV team

Antenatal HIV care should be delivered by a multidisciplinary team (MDT), the precise composition of which will vary. The minimum team would comprise an HIV specialist, obstetrician, specialist midwife and paediatrician, with the recommendation of peer and voluntary sector support. All efforts should be made to involve the woman's GP and health visitor. It may be necessary to involve some of the following: patient advocates, social workers, legal advocacy, clinical psychologists, psychiatrists, counsellors, health advisors, Citizens Advice Bureau (CAB) workers, interpreters, community midwives, clinical nurse specialists and health visitors [56]. In settings with relatively few HIV-positive pregnant women it is still important to develop robust pathways of care with identified members of an MDT. Regular links, formal or informal, could then also be established with a larger unit to provide advice and support as necessary. Good communication is vital in view of the complexity of the issues involved. An early assessment of the social circumstances of a newly diagnosed HIV-positive woman is important. Patients who initially refuse interventions or default from out-patient follow-up need to be identified and actively followed up with particular care.

7.2 Peer support

Support by trained peer-support workers is a valuable component of the management of HIV-positive pregnant women. Many newly diagnosed HIV-positive pregnant

women are initially reluctant to engage with peer support; however, the great majority of women who do engage with it find that it becomes one of the most highly valued of all the interventions that they undertake [57].

7.3 Disclosure of HIV

The importance of informing appropriate healthcare workers should be emphasized. This includes midwives, GPs, health visitors and paediatricians. The process of in-patient care should be explained clearly so that the women can be helped to inform ward staff explicitly about levels of disclosure to visitors.

Levels of disclosure of newly diagnosed pregnant women about their HIV status to their partners vary from 30 to 75% depending on the setting [56,58,59]. Disclosure should be encouraged in all cases but may be viewed as a process that may take some time [60,61]. There are situations where a newly diagnosed HIV-positive woman refuses to disclose to a current sexual partner, or appears to want to delay disclosure indefinitely. This can give rise to very complex professional, ethical, moral and, potentially, legal situations. There is a conflict between the duty of confidentiality to the index patient and a duty to prevent harm to others. Breaking confidentiality in order to inform a sexual partner of the index patient's positive HIV status is sanctioned as a 'last resort' by the World Health Organization (WHO), General Medical Council (GMC) and British Medical Association (BMA) [62–64]. However, it is not to be taken lightly as it could have the negative impact of deterring others from testing because of the fear of forced disclosure and loss of trust by patients in the confidential doctor-patient relationship. Difficult disclosure cases should be managed by the MDT. It is important to accurately record discussions and disclosure strategy in difficult cases.

Simultaneous partner testing during the original antenatal HIV test should be encouraged wherever possible as couples will frequently choose to receive their HIV test results together, providing simultaneous disclosure.

Reassurance about confidentiality is extremely important, especially regarding family members and friends who may not know the diagnosis but are intimately involved with the pregnancy. Women from communities with high levels of HIV awareness may be concerned about HIV 'disclosure-by-association' when discussing certain interventions, including taking medication during pregnancy, having a Caesarean section, and avoiding breastfeeding. Possible reasons such as the need to 'take vitamins', or having 'obstetric complications' and 'mastitis' may help the women feel more confident in explaining the need for certain procedures to persistent enquirers [65].

7.4 HIV serodiscordance and antenatal HIV testing

Between 20 and 80% of newly diagnosed HIV-positive pregnant women may have partners who are HIV negative, depending on the setting [56,58,66]. Such couples require advice regarding condom use and post-exposure prophylaxis following sexual exposure (PEPSE) (www.bashh.org/).

7.5 Welfare and immigration

Many HIV-positive women will have issues relating to social support needs and/or immigration issues. In both cases it is important to identify the issues as early as possible so that women can be referred for appropriate specialist advice and support. Dispersal is an issue that arises and is generally felt to be inappropriate in pregnant women, especially if they are late in pregnancy or are recently delivered [67,68].

7.6 Formula-feeding support

Women with very limited funds should have access to supplementary formula feed [69].

7.7 HIV testing of existing children

This issue should be raised with all newly diagnosed pregnant women who have other children. Absence of symptoms does not imply HIV negativity even in teenage children. In practice the testing of these children is often most easily done when the newborn is attending paediatric follow-up for HIV diagnostic tests.

7.8 Adherence to antiretroviral therapy

This is of vital importance for the success of therapy, and pregnant women may need extra support and planning in this area, especially if there are practical or psychosocial issues that may impact adversely on adherence. Referral to peer support workers, psychology support and telephone contact may all be considered.

7.9 Resistance to intervention

Rarely, women may choose to refuse any intervention during pregnancy or declare their intention to breastfeed the baby against advice. Common reasons may include fear of accepting their HIV status, religious reasons, fear of disclosure to partners, and other family members forbidding the woman from taking up interventions. In cases where the woman threatens to breastfeed against advice it may become a child protection issue, once the child is born.

These cases are very rare but should be discussed with Social Services pre-delivery so that a strategy can be developed.

7.10 Eligibility for treatment

Legislation concerning eligibility to free NHS healthcare in the UK changed in 2004. Patients who have been resident in the UK for 12 months no longer have an automatic entitlement to free care in the NHS. There is an exclusion for 'immediately necessary care' and it could be argued that treatment of an HIV-positive pregnant woman falls within this category. Unfortunately this has been interpreted differently within different Trusts, in some cases denying free treatment and thereby putting the health of mothers and their unborn babies at risk. No hospital should refuse treatment for HIV-positive pregnant women to prevent transmission of HIV to the baby. However, it is possible that women who are otherwise ineligible for free NHS care may be liable for charges subsequently.

It is advisable to get advice from colleagues, the GMC, BMA and Medical Defence Organizations in difficult cases. Legal advice can also be sought from organizations such as the Terrence Higgins Trust (THT) (www.tht.org.uk).

- www.tht.org.uk/informationresources/publications/policybriefingpapers/accesstohivservices.pdf
- www.nat.org.uk/download?rootDocumentId=109&eid=U57GRTWCNZKHM
- www.nat.org.uk/document/253

7.11 Postnatal issues

Postnatal depression is relatively common in the general population, tends to be under-diagnosed and is a risk in HIV-positive women. Women with, or at risk of, antenatal depression should be assessed early and referred onward appropriately.

8.0 Viral load and resistance

8.1 HIV viral load

The risk of mother-to-child transmission correlates with maternal viral load even among women receiving ART [70–72]. Although the risk is greatest for those pregnant women with high viral loads, transmission can occur even when maternal viral loads are below the lower detection limit of the assay [73–75]. Although there is no evidence for a threshold below which transmission will not occur, low or undetectable maternal viral loads are associated with very low rates of transmission to the infant. A

transmission rate of 0.1% (three of 2117 patients) was observed in the UK and Ireland cohort when the HIV viral load was <50 copies/mL plasma on HAART [4]. Studies have generally demonstrated a correlation between viral load in plasma and that in cervicovaginal secretions [52,76]; however, the viral load may sometimes be higher in the genital tract than in the blood and virus may even be shed in this compartment when the plasma viral load is undetectable [54]. Responses to ART and selection of drug-resistant variants may differ between plasma and cervicovaginal secretions [77] and there is evidence of genetic diversity between viral populations in the blood and female genital tract which could account for this [78–80]. Consequently, plasma viral load may not always reflect activity of HIV in the genital tract and this could account for those rare cases of perinatal transmission in women with low or undetectable plasma viral load [74].

A number of commercial assays are available for quantification of HIV-1 RNA, the most widely used in the UK being the Bayer Versant HIV-1 RNA 3.0 branched chain DNA (bDNA) assay, the Roche Cobas Ampliprep/Cobas Taqman system and the Abbott Real Time HIV-1 assay. Although the results of these assays have been shown to correlate, HIV RNA copy number may vary by approximately 0.5–1.0 log₁₀ [81,82]. In order to ensure reliable and accurate quantification of HIV-1 RNA the same assay should be used to monitor viral load unless a lack of sensitivity is suspected. Real-time PCR can qualitatively detect HIV RNA to between 10 and 40 copies/mL. However, there are as yet no data on the significance of detecting HIV at viral loads below 50 copies/mL as a risk for mother-to-child HIV transmission.

In the UK, 78% of HIV infections among women attending antenatal clinics are with non-B subtypes, 61% being subtype A and 29% subtype C [83]. Accurate quantification of non-B subtypes of HIV-1 is therefore an important requirement for monitoring pregnant women. Mismatches between primers and probes used in some commercial assays and RNA target sequences may occasionally result in falsely low or undetectable viral loads among individuals infected with divergent subtypes [84–86]. This appears to be less of an issue, however, with the new generation of commercial viral load assays. Nevertheless, in cases where there are discrepancies among viral load, CD4 cell count and clinical status it is advisable to re-test with another assay in which different nucleotide sequences are used to bind or amplify target RNA. Although rare, some untreated individuals may consistently have an undetectable viral load in conjunction with low CD4 cell counts [87,88]. It has been demonstrated that this is not necessarily assay- or subtype-related and the reason for this discordance remains unclear.

For patients initiating or changing failing therapy, plasma viral load should be monitored 2 weeks after commencing treatment and ideally every 4 weeks thereafter. For patients conceiving on therapy, with undetectable viraemia, viral load measurements every 3 months and at 36 weeks' gestation (depending on turnaround time) may be sufficient. Viral blips are known to occur during suppressive therapy and are of uncertain significance, but the pregnant patient should be recalled and the assay repeated. The viral load at 36 weeks is important when deciding mode of delivery. Knowing the viral load at delivery is helpful in understanding the rare cases of transmission.

8.2 Antiretroviral drug resistance

A baseline resistance assay should be performed on all pregnant women at diagnosis and a further test undertaken following START. Ideally, in women taking ZDV monotherapy, this should be performed on the viral load sample taken at delivery. For women who have received HAART, this should be performed on the first viral load sample taken off therapy, ideally within 6 weeks. Any pregnant woman on nonsuppressive ART should have a resistance test conducted [89,90].

Current commercial assays are based on population sequencing and will not detect minority species representing less than about 20% of the viral population. Such minority drug-resistant variants may persist and impact on future treatment options. As with viral load assays, commercial resistance assays have been developed using the B subtype of HIV and non-B subtypes may therefore be amplified and sequenced less efficiently.

There is concern that the use of ZDV monotherapy in pregnancy may lead to the emergence of drug-resistant virus, possibly compromising the mother's future care. Early studies demonstrated ZDV-associated resistance mutations in approximately 10–25% of pregnant women, with high-level resistance in 6–12% [91–94]. However, in these studies maternal viral loads were generally higher and exposure to ZDV more extensive than would be expected when using ZDV monotherapy according to these guidelines. In the AIDS Clinical Trials Group (ACTG) 076 trial the prevalence of any mutations associated with decreased susceptibility to ZDV was only 3% and no high-level resistance was detected [95]. Similarly, no mutations were detected among women in Côte d'Ivoire receiving short-course ZDV monotherapy initiated late in pregnancy [96]. A UK study [97] also demonstrated that resistance to ZDV was uncommon (5%) and restricted only to those women treated before 1998 who had higher baseline viral loads than those treated between 1998 and 2001, when ZDV monotherapy was only recommended to selected women.

More recently, studies on this cohort have been extended and have demonstrated no evidence of minority species resistant to ZDV [98]. The risk of developing ZDV resistance is therefore likely to be low if monotherapy is restricted to drug-naïve asymptomatic women, with low viral loads and good CD4 cell counts (see Section 10). In a London study, women starting triple ART following ZDV monotherapy were no less likely to have fully suppressed viral replication during 30 months of follow-up post-delivery than women treated with triple combinations during pregnancy [99].

The long half-life of NVP and its low genetic barrier contribute to development of resistance, and this has implications for its use as a single-dose intervention or in a short-term HAART regimen. In the Ugandan HIVNET 012 study [100], drug-naïve women received a single dose of NVP at the onset of labour and their infants a single dose within 72 h of delivery. NVP resistance was detected in 19% (21 of 111) of women at 6 weeks postpartum and was associated with higher baseline viral loads and lower CD4 cell counts [101]. Detectable resistance appeared to be transient, with these mutations no longer found in plasma 12–24 months postpartum. More recent studies have demonstrated resistance in as many as 40% of women following single-dose NVP [102]. Following single-dose NVP, resistance is more frequently detected in women with subtype C HIV infection compared with subtypes A and D [103]. Resistance to NVP can also occur when a single dose is given to women already receiving combination anti-retroviral treatment, the prevalence of the K103N mutation being approximately 15% [104]. Resistance developed in a significant proportion of women receiving a short-term NVP-containing regimen in pregnancy, despite the use of a dual NRTI tail [105]. The high genetic barrier to resistance of boosted PIs and their short plasma half-life make them a more attractive option for START than NNRTIs.

Transmission of drug-resistant virus to the infant can occur [106]. Among infected children the prevalence of ZDV-associated resistance mutations, as a result of perinatal transmission, has ranged from 9 to 17% in some studies [93,94,107], and from 30 to 40% in others [108,109]. Similarly, NVP-resistant virus was detected in 11 of 24 (46%) infected infants in the HIVNET 012 study [101]. However, mutations were transient and no longer detected 4–12 months after delivery. The implication of these mutations, and their subsequent 'fading', for the further management of these children is uncertain. Although some studies have indicated that drug resistance is not necessarily associated with an increased risk of perinatal transmission [92,93,95,107] there is still insufficient information to define clearly the relationship between drug-resistant mutants and mother-to-child transmission.

9.0 Management of HIV-related complications in pregnancy

The health and survival of the mother are paramount. The investigations of a pregnant woman are essentially no different to normal and should be conducted promptly. The usual precautions relating to X-ray exposure apply whether a woman has HIV or not, but unnecessary avoidance of simple investigations can be harmful. Magnetic resonance imaging (MRI) may be safer than computed tomography (CT): discuss with your radiologists.

Most treatments of HIV-related disease are the same regardless of whether the woman is pregnant.

The therapeutic needs of all women of child-bearing potential should be regularly reviewed, particularly now that PCP and other prophylactic therapies can be safely discontinued as immune function recovers.

BHIVA treatment guidelines of opportunistic infections will soon be available and will include a section on pregnancy.

9.1 *Pneumocystis carinii* pneumonia prophylaxis

In a multicentre retrospective study of 148 infants exposed to ART *in utero*, the risk of congenital malformation was found to be significantly raised in those exposed in the first trimester to folate antagonists used for *Pneumocystis* pneumonia prophylaxis combined with ART [110]. In addition to neural tube defects, first trimester exposure to folate antagonists has been associated with an increased frequency of cardiac and renal tract malformations. Regular administration of even small doses of folic acid (such as found in some multivitamin preparations) appears to negate this additional risk [111]. Co-trimoxazole remains the PCP prophylaxis of choice for pregnant women.

10.0 Antiretroviral therapy in pregnancy: efficacy

More than 20 compounds are currently licensed by the Medicines Control Agency for the specific treatment of HIV-1 infection in the UK. Of these, only ZDV is specifically indicated for use in pregnancy.

The Cochrane Systematic Review, which was restricted to interventions shown to be effective in randomized controlled trials, concluded that ZDV monotherapy, NVP monotherapy and delivery by elective Caesarean section (PLCS) appear to be very effective in decreasing the risk of transmission [112], while in the 2007 update the authors conclude that 'a combination of zidovudine plus 3TC given to mothers in antenatal, intrapartum and postpartum periods and to babies for a week after delivery or a single

dose of NVP given to mothers in labour and babies immediately after birth may be most effective' [113]. This clearly does not reflect current practice but is extremely helpful in drawing attention to the lack of clinical trial data with HAART in pregnancy. The question of efficacy relates to reducing infections in the neonate, maintaining or improving maternal health and preserving maternal therapeutic options.

10.1 Evidence of efficacy from monotherapy studies

10.1.1 Zidovudine

The efficacy of ZDV to reduce mother-to-child transmission of HIV-1 has been demonstrated in several large randomized controlled studies [71,114,115] and supported by epidemiological surveys [116–119]. The efficacy of ZDV ranges from 67%, when started before the third trimester, administered by intravenous infusion during labour, and given to the neonate for the first 6 weeks of life, to 50% with shorter courses (started at week 36), without a neonatal component, in nonbreastfed babies, to 30% with a similar regimen in breastfed babies [120,121]. In a nonbreastfeeding population the transmission rate with ZDV monotherapy has been reduced to 6–8% [114,117]. As with monotherapy in nonpregnant women ZDV transiently reduces HIV-1 plasma viraemia and increases CD4 positive lymphocyte counts. In PACTG 076, in which mothers commenced ZDV 100 mg five times daily between weeks 14 and 28 of gestation, therapy was associated with a 0.24 log₁₀ reduction in plasma viraemia at the time of delivery [75,117]. In the Bangkok study, ZDV 300 mg twice daily was commenced at week 36 resulting in a 0.57 log₁₀ reduction in plasma viraemia at delivery. This was considered to account for 80% of the efficacy of ZDV in reducing transmission [71] (Table 1).

Viral load is an important predictor of transmission and ZDV reduces transmission at all levels of maternal viraemia. However, in mothers with untreated very high viral load (> 100 000 RNA copies/mL) the transmission rate may be >60% and therefore, even with a two-thirds reduction in transmission, the risk to the infant would still be high. HAART is therefore recommended for any mother with a viral load >10 000 copies/mL (see also Scenarios). PLCS has been demonstrated to reduce transmission by as much as ZDV (see Section 10). When ZDV and PLCS were combined, in a cohort of women with all levels of viral load, transmission was further reduced to <1% [122]. The Agence Nationale de Recherche sur le SIDA (ANRS) French Perinatal (1997–2004) Cohort had an overall transmission rate of 1.3% with no significant difference in transmission rates among HAART, dual therapy and monotherapy, but details of mode of delivery for each therapeutic group were

not presented [123]. In the UK and Ireland, the observed transmission rate in women on ZDV monotherapy plus PLCS was 0% (0 of 467 patients; 95% upper CI 0.8%). This was not significantly different from the 0.7% transmission rate with HAART plus PLCS (17 of 2337 patients; 95% CI 0.4–1.2%) or the 0.7% rate with HAART and a planned vaginal delivery (four of 565 patients; 95% CI 0.2–1.8%) [4].

10.1.2 Nonnucleoside reverse transcriptase inhibitors

The rapid placental transfer and long half-life of NVP have led to studies of the efficacy of NVP to reduce the risk of mother-to-child transmission of HIV. In HIVNET 012, NVP given to the mother in labour and to the neonate reduced transmission up to 18 months despite ongoing breastfeeding [100,124]. The efficacy of this approach was confirmed by the South African Intrapartum Nevirapine Trial (SAINT) study [125]. The efficacy, low cost and ease of use led to its adoption by WHO. However, the use of two-dose NVP alone to prevent mother-to-child transmission of HIV is now reserved for only those settings where more intensive interventions are not available because of the development of resistance, which has been shown to impact on the response to subsequent NNRTI-containing HAART [126,127]. The use of single-dose nevirapine (NVP) as an emergency in labour may be appropriate in certain situations (see Scenarios) provided that sufficient cover of the pharmacological tail is provided.

As efavirenz also has a plasma half-life that is at least as long as that of NVP, similar problems with resistance might be anticipated if it is used as either short-course or single-dose therapy.

10.2 Evidence from studies of combination therapy

10.2.1 Dual nucleoside reverse transcriptase inhibitor therapy

While cohort data have shown lower rates of transmission with ZDV plus 3TC (2.6%) than with ZDV alone (6.5%) [109], concerns relating to 3TC resistance outweigh these benefits and this approach is therefore not recommended.

10.2.2 Zidovudine monotherapy with single-dose nevirapine and 1 week of zidovudine plus lamivudine

The current practice, as advocated by WHO in resource-limited settings [128], of adding single-dose NVP to short-course ZDV (from 28/40) reduces transmission to 2% in formula-feeding mothers [129]. The high rates of mutations associated with NVP resistance can be considerably reduced if the period of pharmacological activity is covered, as recommended, with ZDV plus 3TC for 1 week [130] (see Section 8). Low rates of NVP mutations were also

Table 1. Evidence of the efficacy of antiretroviral therapy to reduce the risk of mother-to-child transmission of HIV infection, from studies in (a) nonbreastfeeding populations and (b) breastfeeding populations

Study name	Countries	Study size	Treatment components			Age HIV assessed	Transmission rates (%)	Percentage reduction (P)
			Prepartum (initial gestation, weeks)	Intrapartum (i.v./oral)	Postpartum (weeks)			
(a)								
PACTG 076/ANRS 024 [114]	France USA	402	14–34 ZDV 100 mg 5 × daily	i.v. ZDV	6 ZDV	18 months (antibody)	22.6 placebo 7.6 ZDV	66.3% (0.00006)
Bangkok Trial [71]	Thailand	392	36 ZDV 300 mg bid	Oral ZDV	Nil	6 months DNA PCR	18.9 placebo 9.4 ZDV	50% (0.006)
PHPT [115]	Thailand	1437	ZDV 300 mg bid	ZDV	ZDV	180 days DNA PCR	6.7	57.6% cf short/short interim (0.004)
Long/long arm			28	Oral	6		5.7	
Short/long arm			35	Oral	6		8.4	
Long/short arm			28	Oral	3 days		10.6 (discontinued)	
Short/short arm			35	Oral	3 days			
AI455–094 [178]	Soweto	197	34–36		6 weeks	6 weeks		Equivalence between ZDV and d4T combined with ddl
			ZDV 300 mg bid	ZDV	ZDV	DNA PCR	6.3	
			d4T 40 mg bid	d4T	d4T		4.2	
			ddl 200 mg bid	ddl	ddl		1.9	
			d4T and ddl	d4T and ddl	d4T and ddl		2.0	
PMCT-2 [129]	Thailand	1844	28 weeks ZDV	Oral ZDV	1 week ZDV		1.9	
				sdNVP	sdNVP v placebo		2.8	
				sdNVP			6.5	
				Placebo				
Study name	Countries	Study size	Treatment components			Age HIV assessed	Transmission rates (%)	Percentage reduction (P)
			Prepartum (initial gestation week)	Intrapartum (i.v./oral)	Postpartum (weeks)			
(b)								
RetroCI [120]	Côte d'Ivoire	280	36 ZDV 300 mg bid	Oral	Nil	3 months 6 months 12 months 18 months 24 months	26.1 vs. 16.5 26.1 vs. 16.9 28.5 vs. 18.5 30.1 vs. 21.6 30.1 vs. 22.1	37% (0.07) 35% 35% 28% 27% (< 0.5)
DITRAME [308]	Burkina Faso, Côte d'Ivoire	431	36 ZDV 300 mg bid	Oral	1 week maternal	6 months	27.5 vs. 18	35%
PETRA [303]	RSA, Tanzania, Uganda	1802	36 ZDV 300 mg bid 3TC 150 mg bid	Oral	Yes	15 months 6 weeks 18 months	30.6 vs. 21.5 17.2 vs. 8.6 26.6 vs. 20.7	30% 50% (0.001) 22% (0.07)
			Nil	Oral	Yes	6 weeks 18 months	17.2 vs. 10.8 26.6 vs. 24.4	37% (0.02) 8% (0.5)
			Nil	Oral	Nil	6 weeks 18 months	17.2 vs. 17.7 26.6 vs. 25.7	– 3% (0.8) 3% (0.8)
HIVNET 012 [309]	Uganda	626	Nil	ZDV 300 mg stat + 3-hourly vs. NVP 200 mg stat	ZDV 7 days vs. NVP stat 48 < 72 h	6–8 weeks 12 months	ZDV vs. NVP 20.0 vs. 11.8 24.1 vs. 15.7	41% (0.006) 35%
SAINT [125]	RSA	1307	Nil	Oral ZDV + 3TC vs. NVP	1 week	8 weeks	ZDV + 3TC vs. NVP 10.8 vs. 14	Equivalence

PACTG, AIDS Clinical Trials Group; ANRS, Agence Nationale de Recherche sur le SIDA; bid, twice daily; d4T, stavudine; ddl, didanosine; DITRAME, Diminution de la Transmission Mere-Enfant; HIVNET, HIV Network for Prevention Trials; i.v., intravenous; NVP, nevirapine; PETRA, PErinatal TRAnsmision trial; PHPT, Programme for HIV Prevention and Treatment; PMCT, Prevention of Mother-to-Child Transmission; RetroCI, RETRO – Cote d'Ivoire; RSA, Republic of South Africa; SAINT, South African Intrapartum Nevirapine Trial; sdNVP, single-dose nevirapine; 3TC, lamivudine; ZDV, zidovudine.

seen when single-dose NVP was given on a background of ZDV plus 3TC from 34 weeks [131] but higher rates of 3TC resistance (8.3%) occurred and the strategy did not significantly improve mother-to-child transmission rates compared with ZDV monotherapy with single-dose NVP [132]. These approaches are not recommended as first-line interventions in the UK.

10.3 Combinations with more than two drugs

In the North American Women and Infants Transmission Study (WITS) cohort there has been a reduction in transmission from 7.8% in mother–infant pairs receiving ZDV monotherapy to 1.1% in mother–infant pairs exposed to triple therapy including a PI [5]. In Pediatric AIDS Clinical Trials Group (PACTG) 367 the transmission rate among 3081 pregnant women delivering in North America fell from 4.2% in 1998 to 0.5% in 2002. Among women who received no ART, transmission was 18.5%, falling to 5.1% with ZDV monotherapy, 1.4% with dual NRTIs and 1.3% with three or more drugs. Of the 1736 women who had plasma viraemia of <1000 copies/mL at the time of last measurement prior to delivery, the transmission rate was 0.7% [133].

Data from the elective Caesarean section (ECS) demonstrate a reduction in transmission over time periods that can be associated with changing trends in therapy from ZDV monotherapy for all, to dual therapy and finally to HAART. In the period 2001–2003, during which time 92% of mothers received HAART, HIV transmission was reduced to 0.99% (95% CI 0.32–2.3%) [134].

Transmission at <50 copies/mL plasma at delivery has been reported, with a rate of 0.4% (five of 1338 patients) in the ANRS French Perinatal Cohort [123] and 0.1% (three of 2117 patients) in the UK and Ireland cohort [3,4].

In summary, although these studies show a reduction in transmission since the introduction of HAART, recent data from the UK show no difference in transmission rates, when comparing mothers given ZDV monotherapy combined with PLCS, according to BHIVA guidelines, and those receiving HAART [3].

10.4 Stopping HAART

Where therapy is not required during pregnancy for maternal health, combinations of three or more drugs to suppress HIV replication may be prescribed short term to reduce transmission without compromising future maternal therapeutic options. Stopping NVP or efavirenz must be carefully planned with appropriate tails, to allow for their long half-lives.

11.0 Antiretroviral therapy in pregnancy: toxicity

11.1 Maternal toxicity

Information about the safety of drugs in pregnancy is limited. Data are usually from animal studies, anecdotal experience, registries and clinical trials.

11.2 Nucleoside reverse transcriptase inhibitors

NRTIs are generally well tolerated in pregnancy; reported incidences of adverse effects are similar to those reported in nonpregnant HIV-infected individuals. In the French cohort most of the adverse events seen in mothers taking ZDV plus 3TC were related to pregnancy or postpartum complications of pregnancy [109].

NRTIs may cause mitochondrial dysfunction as they have varying affinity for mitochondrial DNA γ polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion [135]. The relative potency of NRTIs in inhibiting mitochondrial DNA γ polymerase *in vitro* is highest with zalcitabine, followed by didanosine, stavudine, 3TC, ZDV, abacavir, tenofovir and emtricitabine [136]. The mitochondrial toxicity of ZDV may, however, not be entirely related to mitochondrial DNA γ polymerase inhibition. Lamivudine, abacavir, tenofovir and emtricitabine have been shown to have relatively low toxicity in this regard. Toxicity related to mitochondrial dysfunction has been reported in patients receiving long-term treatment with NRTIs and, although this generally resolves with discontinuation of the drug or drugs, fatalities have been reported.

Early in 2001, the US Food and Drugs Administration and the European Medicines Authority advised doctors that they had received reports of three pregnant women who had died of lactic acidosis following treatment with stavudine and didanosine (as part of triple therapy) and a further four cases of lactic acidosis in pregnancy with this combination [137]. The use of didanosine plus stavudine in pregnancy should be restricted to women with resistance or intolerance to other NRTIs and no reasonable alternatives. Monitoring liver function and blood lactate in pregnant women on this combination is therefore recommended.

11.3 Protease inhibitors

Hyperglycaemia, new onset diabetes, exacerbation of existing diabetes mellitus and diabetic ketoacidosis have been reported with administration of PIs [138,139]. Women taking ART that includes a PI reportedly have a higher risk of developing diabetes mellitus during pregnancy (3.5%)

than HIV-negative women or HIV-positive women either taking NRTIs or on no therapy (1.35%) ($P = 0.025$) [140]. In a Spanish cohort of 609 pregnant women with HIV infection the incidence of gestational diabetes (GD) was 7% (higher than expected for the general population). Older age and use of PI [odds ratio (OR) 2.3; 95% CI 1.0–5.3] were associated with GD in a multivariate analysis [141]. Higher rates of hyperglycaemia were also seen with nelfinavir (15.6%) than with NVP (8.6%) in a Dutch study [142]. However, this has not been found in other cohort reviews [143,144] nor in a recent prospective study comparing 76 women taking PI-based therapy (33% had impaired glucose tolerance) with 73 women on a PI-sparing regimen (26% had impaired glucose tolerance) [145]. Thus the data remain inconclusive.

Indinavir and full-dose ritonavir are now rarely prescribed in general HIV care and are not considered further here. Nelfinavir has been widely prescribed and was well tolerated in 128 pregnant women although gastrointestinal side effects (29.7 *vs.* 6.6%) and hyperglycaemia (15.6 *vs.* 2.2%) were significantly more common compared with nonpregnant women in the same cohort [142]. Nelfinavir is no longer available in Europe because of concerns regarding impurities. There are plans to construct a register of children exposed to nelfinavir and women who have taken nelfinavir during pregnancy. Details can be obtained from www.emea.europa.eu, www.rocheuk.com or www.chiva.org.uk. Data regarding unboosted saquinavir are sparse. Although a significant proportion of mothers (13 of 42; 31%) developing abnormal liver function tests (LFTs) with ritonavir-boosted saquinavir has been reported, all but one were grade 1/2 and therapy was only changed in five of these patients [146]. Ritonavir-boosted lopinavir was well tolerated in a retrospective study of 104 mothers in the UK, with 96 continuing therapy to delivery. Nausea and vomiting were reported by 26% but <2% discontinued therapy. Grade 1/2 abnormal LFTs were also common (19.2%) with grade 3 changes in 3.8%, but only one patient, with pre-eclampsia, stopped therapy. Hyperglycaemia was uncommon (<2%) [147]. Limited data (33 pregnancies) have been presented on atazanavir. Although maternal bilirubin levels were nearly always (92%) elevated (range 4–76 $\mu\text{mol/l}$) no infants required phototherapy [148].

11.4 Nevirapine

The main concerns with NVP relate to cutaneous and hepatic toxicity. There has been a change to the Summary of Product Characteristics (13 February 2004) which, along with other changes, now states that 'women and patients with higher CD4 cell counts are at increased risk of hepatic

adverse events, often associated with rash, especially women with pre-treatment CD4 counts >250 cells/mm³. Although there is no specific mention of pregnancy, pregnant women are perhaps more likely to match this description than nonpregnant women, especially those choosing short-course therapy. Whether the risk of hepatitis is the same in pregnancy is uncertain but a number of hepatitis-related deaths have been reported in pregnant women taking regimens that include NVP [149], including two cases reported from a cohort of 123 women in Ireland who initiated an NVP-containing regimen during pregnancy. These patients were treated according to Irish Guidelines for the Management of HIV in pregnancy which recommend that all pregnant women should be treated with HAART [150]. Both fatalities occurred in women with high CD4 counts (473–501 cells/ μL) and low viral loads (724–1895 copies/mL) [151]. Neither woman would have initiated NVP since the change in summary of product characteristics (SPC). In PACTG 1022, four of 17 women discontinued NVP because of toxicity compared with one of 21 women randomized to nelfinavir. One patient treated with NVP, whose baseline alanine aminotransferase (ALT) was 58 U/L, died of fulminant hepatic failure [152]. Money *et al.* reported 'major' toxicities in six of 57 women (10.5%) taking NVP during pregnancy compared with one episode of renal calculi among 47 women taking a PI (2%) [153]. Conversely, Bershoff-Matcha *et al.* [154] reported no serious adverse events among 43 pregnant women compared with 23 among 227 nonpregnant women. Natarajan compared 170 women who commenced NVP during pregnancy with 65 pregnant women who had commenced NVP prior to conception. The incidence of rash (7.6%) and hepatitis (4.7%) during the pregnancy was higher in those initiating NVP than in those who had started earlier (rash 3.1%), but alternative causes for the suspected toxicity were found in seven cases and only 10 mothers (5.8%) discontinued NVP. There were no deaths [155]. In a study of 126 women commencing NVP-based HAART in Thailand, eight (6.3%) developed hepatitis of whom six discontinued NVP and nine (7.1%) developed a rash of whom six discontinued NVP. No statistically significant difference in frequency of complications was seen in the women commencing NVP-based HAART with a CD4 count >250 cells/ μL (14.5%) compared with those starting at <250 cells/ μL (12%) but the treatment time was shorter in the latter group who started therapy at 28 weeks of gestation [156]. In a Thai population that included men, pregnant women and nonpregnant women, 9.4% starting NVP as part of triple therapy developed liver or skin toxicities; pregnant women with CD4 counts >250 cells/ μL did not have significantly higher rates [157]. Data presented at the Conference on Retroviruses and Opportu-

nistic Infections 2007 suggested that, in pregnant Thai women, prescription of NVP for women with CD4 cell counts up to 350 cells/ μ L remains safe [158]. These conflicting data are likely to be attributable to differences in populations, small sample size and reporting bias, especially if the outcomes for patients starting therapy during pregnancy are mixed with those for patients continuing therapy during pregnancy. In the Kisumu study in Kenya, in which ZDV, 3TC and NVP are started at 34 weeks' gestation, 13 of 155 (8.4%) mothers had to stop NVP with grade 2–4 toxicities, but a CD4 count cut-off of 250 cells/ μ L did not discriminate between susceptibility states [159]. Therefore, although severe toxicity and fatalities were reported in some pregnant women starting NVP in pregnancy, data from several much larger cohorts [155,158,159] including 563 mothers have not shown that pregnant women are at greater risk.

In conclusion, NVP has been widely prescribed and shown to be effective in pregnancy and remains a useful component of HAART in pregnancy. Only nelfinavir (as the third drug in a dual NRTI backbone) has been used to a similar degree. There is very little reported experience with other triple therapies in pregnancy. All the studies have shown combination therapy to be effective in reducing mother-to-child transmission and therefore the potential benefits of the intervention must be assessed against the risk of toxicity.

11.5 Pregnancy outcome

There are a number of studies, including studies from the UK, that show a significant association between the use of HAART in pregnancy and pre-term delivery (PTD).

The possibility that PI use was associated with an increased risk of PTD had been suggested by Swiss investigators in 1998 [160]. In an analysis of data from the combined Swiss and European Collaborative Study cohorts, further evidence of an increased rate of PTD was found in women on combination ART including a PI [161]. In the 2004 analysis of this ongoing study, a trend towards more PTDs (in women not delivering by PLCS) was shown over time, correlating with increased use of combination therapies [162]. Data from the UK and Ireland on 4445 pregnancies with delivery between 1990 and 2005 showed that 13% of deliveries were before 37 weeks with a 1.5-fold increased risk if the mother took HAART during pregnancy compared with ZDV monotherapy (or dual therapy) [163] and the association was stronger for more severe PTDs.

An Italian study suggested that HAART in pregnancy is associated with a reversal of the T helper type 1 (Th1) to Th2 switch that is a feature of normal pregnancy [164].

Two further questions arise: are all HAART regimens equal; and does the timing of initiation of therapy matter? A number of studies report a trend towards more PTDs with PIs than with NVP-based therapy and this needs further clarification. If PTD is related to changes in cytokine profiles, as suggested by Fiore's study of women already taking HAART at conception [164], then initiating HAART in pregnancy might exacerbate this effect. Data from a study by Martin and Taylor suggest that this may be the case, with a much higher rate of PTD (20%) among pregnant women initiating HAART during pregnancy, regardless of indication (i.e. maternal health *vs.* prevention of mother-to-child transmission), than in women who conceived on HAART (9.5%) or who took ZDV monotherapy (5.8%) [165]. Finally, it is worth noting that 60% of the PTDs were defined as severe, that is, delivering prior to week 34. However, in the Amsterdam and Rotterdam (AmRo) study [166] the most striking association was with therapy commenced early or before pregnancy, although there was no evidence for this in the study on the UK and Ireland cohort [163].

The experience in North America seems to differ from that in Europe. Much higher rates of PTD are found in the general population (12.5% in 2004 [167]) and in 1989, when fewer than 50% of the mothers received antenatal care, the PTD rate in HIV-positive mothers was 35% [168]. This has since fallen to 22% but remains considerably higher than in the UK and Ireland (13%). Drug use, symptomatic HIV infection and no ART were significantly associated with PTD in this cohort of more than 11000 pregnancies. In a 1998 North American multicentre study of 76 women taking a PI as part of combination therapy during pregnancy there were 15 PTDs (<37 weeks) but 60% of the mothers had identifiable risk factors for PTD such as a history of PTD, smoking and substance misuse [169]. Among 462 women participating in ACTG studies in 1998–1999 the PTD rate was also 20% but with no significant difference between women exposed to PIs and those not exposed to PIs [relative risk (RR) 0.7; 95% CI 0.5–1.1] while the rate of very premature delivery (<32 weeks) was lower among women taking PIs (RR 0.2; 95% CI 0.05–0.8) [170]. In a meta-analysis of data from several North American cohorts the PTD rate was \sim 17% with no effect of combination ART compared with no ART or monotherapy [171]. However, data submitted voluntarily to the Antiretroviral Pregnancy Register, which mostly include submissions from North America, show a trend to very low birth weight in babies exposed to three or more drugs *in utero* [172]. Recently a North American cohort study did find an association between HAART (three or more effective drugs) and PTD but only for PI-containing combinations [173].

Two published studies have found an increased risk of pre-eclampsia in patients taking HAART: this may form part of the risk of PTD as well as having important maternal and foetal implications [174,175]. This contrasts with the lower-than-expected rate of pre-eclampsia in HIV-infected mothers seen in the pre-ART era [176] but was not seen in a Brazilian study in which, despite high rates of HAART use, the rate of pre-eclampsia in HIV-positive women was 0.8% compared with 10.6% in uninfected controls [177].

While the data on impaired glucose tolerance and PIs are inconclusive and the association of HAART with higher rates of pre-eclampsia unsubstantiated, there is accumulating evidence for an increased risk of PTD and, in particular, severe (<34 or <32 weeks) PTD in mothers taking HAART. While in some mothers this is unavoidable because of maternal health or high viraemia, in others ZDV monotherapy and PLCS may be a safe option.

11.6 Embryonic/foetal toxicity

The Antiretroviral Pregnancy Registry contains a summary of relevant mutagenesis, carcinogenesis and teratogenesis data for each licensed antiretroviral (www.apregistry.com). Reports are updated twice a year. The concerns relating to didanosine and efavirenz are discussed below. No other compounds have yet given rise to any concern.

11.6.1 Didanosine

Ever since the patient denominator for first trimester exposure of 200 was reached in January 2005, the incidence of congenital malformations among babies exposed *in utero* to didanosine has been significantly higher than for any other antiretroviral with similar numbers of exposed babies. Numbers of first trimester exposures (259) are still relatively few compared with ZDV (1643) and 3TC (1888) but the 95% CIs (3.3–9.4%) remain above the expected rate of 'early' congenital malformations (2.4%). The observed incidence of 5.8% also exceeds that observed (1%) with second or third trimester initiation of therapy, although the 95% CI overlap is 0.1–3.7%. No pattern of congenital malformations has been observed but this does not exclude causation. Until this has been resolved it is reasonable to avoid first trimester didanosine exposure.

11.6.2 Efavirenz

The concerns relating to efavirenz date back to pre-clinical animal studies that have not been conducted with any other ART. Twenty cynomolgus macaques were exposed to efavirenz during early pregnancy. Three of the 20 offspring had significant abnormalities at birth: one with anencephaly and unilateral anophthalmia; the second with

microphthalmia; and the third with a cleft palate. Consequently efavirenz was classified as class C and it is recommended that efavirenz should not be prescribed to women of child-bearing potential. These data are likely to have heightened awareness of the potential risk of teratogenicity with this compound. In prospectively reported data to the international, but US-dominated, Antiretroviral Pregnancy Register there have to date (January 2007) been only seven defects noted in 281 babies born following first trimester efavirenz exposure and none has resembled the abnormalities observed in macaques. Efavirenz was, however, reclassified as class D, indicating an established risk to the human foetus, based on three reports of myelomeningocele and one of Dandy–Walker syndrome to the register. Each was reported retrospectively, that is after the outcome of the pregnancy was known, and therefore the relative risk cannot be calculated as the denominator (total number of exposures) is not known. Two of the reported cases of spina bifida and the case of Dandy–Walker syndrome were reported in aborted foetuses. Since the incidence of spina bifida in the USA is 4.3 per 10 000 live births the expected number of cases of spina bifida in the prospectively reported register (6636 pregnancies) is three; however, to date none has been reported. Two further cases of Dandy–Walker syndrome have since been reported in the prospective arm of the register, and one further case of spina bifida has been reported in the retrospective arm: none of these babies was exposed to an NNRTI. Until more robust data are available it remains advisable to avoid efavirenz for women who may conceive.

11.6.3 Management of women who conceive on efavirenz

There are two issues to consider: the gestational age at presentation, and the plasma half-life of efavirenz. After stopping, it can take up to 3 weeks for efavirenz to clear from the plasma. It is not known whether there is a key period during the first 6 weeks of foetal development when efavirenz affects central nervous system (CNS) development and the minimal teratogenic dose is also unknown. In addition, given the long half-life of efavirenz, it is difficult to speculate on whether discontinuing efavirenz after the diagnosis of pregnancy will reduce the risk of spina bifida. The risk of spina bifida, which cannot yet be quantified, the gestational age, and the pharmacokinetics of efavirenz should therefore be balanced with potential advantages of continuing a fully suppressive regimen, especially if options are limited. This should be discussed with any woman who conceives while taking efavirenz. Discontinuing all therapy is not recommended as this potentially exposes the women to efavirenz monotherapy for up to 3 weeks. The neural tube has closed by 6 weeks and therefore

discontinuing efavirenz if the pregnancy is diagnosed after this time will not influence the outcome.

12.0 Antiretroviral therapy and pregnancy: pharmacokinetics

Physiological changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting the drug dosing. During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease, notably albumin and α_1 acid glycoprotein; renal sodium re-absorption increases; and changes occur in the metabolic enzyme pathway in the liver, including changes in CYP450.

A reduced dose of didanosine is usually prescribed combined with tenofovir, but there is increased renal excretion of didanosine in pregnancy. Although this is not considered sufficient to merit dose amendment there are no data on didanosine in pregnancy when prescribed with tenofovir. However, the new European recommendations are that these compounds should not be co-administered, especially in patients with high viral load and low CD4 cell count (Letter to Health Care Professionals from Bristol-Myers Squibb and Gilead, 2 March 2005).

The pharmacokinetics of other NRTIs are generally not affected by pregnancy and dose adjustment is not required [178–183].

Tenofovir concentrations in the third trimester are reduced by about 15% compared with postpartum. Cord blood concentrations are approximately 60% of maternal blood concentrations. The area under the curve (AUC) target of 2 $\mu\text{g h/mL}$ was missed in five of 19 women [184].

NVP has been studied in pregnancy and plasma concentrations are similar to those in nonpregnant adults [185–187]. No dose adjustment is required.

PIs are highly protein-bound and placental transfer in humans appears to be limited. During the third trimester of pregnancy, lopinavir remains 99.04% protein-bound, which means that there is 17% more protein-free lopinavir [188].

Nelfinavir concentrations tend to be variable and frequently low [189]. Nelfinavir is currently not available in Europe.

The plasma concentrations of saquinavir when prescribed as unboosted soft-gel capsules are generally low [190] but when the hard-gel capsules [191], soft-gel capsules [192] or new formulation tablets [193] are boosted by co-prescription with ritonavir, plasma concentrations appear to be generally therapeutic and no dose adjustment

is routinely required. Interpatient variability during pregnancy is, however, high [146].

Compared with postpartum concentrations, third trimester concentrations of lopinavir (lopinavir 400 mg/ritonavir 100 mg) are reduced by 28%. The protein-free fraction is moderately increased (17%) and, at the standard dose, lopinavir appears to be clinically effective with a wide variation in individual plasma trough concentrations. Cohort studies have suggested that the majority of mothers taking the standard adult dose have adequate trough concentrations [194]. Furthermore, these data relate to the Kaletra™ capsule formulation. Until data from the new tablet formulation are available no dose adjustment is recommended as a routine.

At standard dose, boosted atazanavir concentrations are similar in the third trimester and postpartum [126].

In general, there are still limited data on the currently available PI formulations and a protein-binding effect has been examined only for lopinavir. Given this lack of data and the considerable degree of interpatient variability, therapeutic drug monitoring is recommended for PIs during pregnancy. It should be conducted at steady state (2 weeks or more into therapy) and repeated in the third trimester.

The pharmacokinetics in pregnancy of newer agents such as emtricitabine, tipranavir, darunavir fosamprenavir and maraviroc have not been described. There is an urgent need for extensive investigation of the pharmacokinetics of ART in pregnant women to ensure efficacy, to reduce toxicity and to prevent the emergence of resistance through inadvertent underdosing. Therefore, therapeutic drug monitoring in pregnancy should be considered for all PIs and for new agents where the facility exists.

Penetration of PIs into the genital tract of pregnant women is variable. Indinavir appears to concentrate in the cervicovaginal secretions whilst lopinavir and saquinavir could not be detected [127]. The implications of such data are uncertain.

NRTIs penetrate the genital tract more efficiently. A recent study compared genital tract levels with plasma giving values as follows: emtricitabine 600%, 3TC 300%, tenofovir 300% and ZDV 200% [195].

13.0 Obstetric management of pregnancy and delivery

The management of the HIV-positive pregnant woman aims to minimize the risk of mother-to-child transmission while not increasing maternal or neonatal morbidity. It must be recognized that much of the evidence for obstetric factors contributing to mother-to-child transmission comes from the pre-HAART era. There are very few studies to date examining these issues in the setting of women with a fully

suppressed plasma viral load on HAART. As such it is unclear whether a woman with a fully suppressed viral load can be managed as if she were not HIV-infected in all obstetric situations. Until such data are available, it may be prudent to adopt a relatively cautious approach in some circumstances, as reflected by the guidance in this section.

13.1 Antenatal care

The importance of confidentiality, a care plan and a multidisciplinary approach to antenatal care is discussed in Section 7.

Periconceptual folic acid supplements are recommended. This is particularly important for those taking co-trimoxazole (the folate antagonist most commonly used for PCP prophylaxis), as maternal folate deficiency is associated with neural tube defects in the foetus.

The dating and anomaly scans should be undertaken according to national guidelines for the general population [196]. The issue of teratogenicity from first trimester exposure to antiretrovirals is discussed elsewhere but it is appropriate for the anomaly scan to be undertaken by the most experienced operator available. Screening for Down's syndrome should be discussed with all women during the first trimester. Provision of the most specific and sensitive noninvasive tests for Down's syndrome (nuchal translucency with serum screening) with appropriate counselling is likely to reduce the need for subsequent invasive prenatal diagnostic testing (discussed below).

13.2 Early pregnancy problems

13.2.1 Nausea and vomiting

Nausea and vomiting are common in early pregnancy. Symptoms usually begin between 5 and 6 weeks' gestation, and in 90% of women these symptoms have resolved by 16 weeks. The incidence of nausea and vomiting may be increased in women taking HAART. Most women are able to adjust the timing of their antiretrovirals to avoid times of nausea.

Hyperemesis gravidarum is a condition characterized by intractable vomiting leading to fluid and electrolyte disturbances and nutritional deficiency. The onset is always in the first trimester. In severe cases, with inadequate treatment, hyperemesis may cause Wernicke's encephalopathy (as a result of thiamine deficiency), central pontine myelinolysis (as a result of hyponatraemia or its rapid reversal) and maternal death. Hyperemesis is a diagnosis of exclusion. In HIV-positive women, particularly those taking HAART, a diagnosis of hyperemesis should only be made once acidosis, hepatitis and pancreatitis have been excluded. Management of hyperemesis includes intrave-

nous fluid replacement, correction of electrolyte imbalance, thiamine replacement and antiemetics. There is no reported increase in teratogenic risk with standard antiemetic drugs [197,198]. First-line agents include the antihistamines promethazine and cyclizine. Prochlorperazine and metoclopramide may be used as second-line agents, but their use has been associated with extrapyramidal reactions in some young women [197,198]. Oral, rectal and systemic routes of administration should be considered. Controlled interruption of HAART may be the best option in severe cases. There are no known interactions between antiemetics and antiretrovirals.

13.2.2 Bleeding in early pregnancy

Although earlier studies have suggested that HIV infection increases the risk of first trimester pregnancy loss (miscarriage and ectopic pregnancy) [18], more recent studies [199,200] have not confirmed this. Management of HIV-positive women with bleeding in early pregnancy does not differ from that of HIV-negative women with similar symptoms, and many of these women can be managed in early pregnancy units. The possibility of drug toxicity should be considered in women with abdominal pain.

13.2.3 Prenatal diagnosis

HIV-infected women considering invasive prenatal diagnosis should be counselled in a specialist foetal medicine unit. For those women requiring genetic testing by amniocentesis every effort should be made to avoid inserting the needle through the placenta. Observational studies conducted prior to the widespread use of HAART in pregnancy suggested a possible association between amniocentesis and mother-to-child transmission. However, this association has not been demonstrated in more recent studies of women taking HAART [201–203]. For women who have started HAART but whose viral load is not yet undetectable, it may be advisable to delay the amniocentesis until the maternal viral load is undetectable if at all possible. In women not already taking HAART, administration of antiretrovirals to cover the procedure is advised. In these cases, the chosen regimen should ideally include agents with good placental transfer. PIs cross the placenta only to a very limited degree. If NNRTIs are not already part of the regimen consider adding a single 200 mg dose of NVP to other HAART therapy.

13.3 Complications of later pregnancy

13.3.1 Problems associated with HIV

There are a number of medical conditions that may arise as a result of HIV infection and that can complicate the

pregnancy. Some of these complications are known to increase the risk of mother-to-child transmission.

Pregnancy is a hypercoagulable state and infection with HIV may increase this tendency. The adoption of stringent antithromboembolic precautions is essential if a pregnant HIV-positive woman is hospitalized or undergoes surgery. This will include thrombo-embolic deterrent (TED) stockings and/or low-molecular-weight heparin injections.

HIV infection may also be associated with the development of acquired thrombophilias, which in the general population are known to predispose to a range of pregnancy complications such as *in utero* foetal death, pre-eclampsia and intrauterine growth restriction. Although it is thought that these can be managed in a similar fashion to thrombophilias in pregnant women who are not HIV-infected, there are no studies to confirm similar efficacy in HIV-infected women.

Nephropathies associated with HIV infection can occur. One of the commonest is immunoglobulin A (IgA) nephropathy which results in large amounts of protein being lost in the urine. This will increase the risk of pre-eclampsia and hypertension, and is associated with an increased risk of thromboembolism [204].

13.3.2 Medical disorders of pregnancy

Glucose impairment and pre-eclampsia have been associated with ART (see Section 11). Both should be managed as per normal obstetric practice.

Obstetric cholestasis (OC) has a complex aetiology, which includes genetic, environmental and endocrinological factors. It is a diagnosis of exclusion but is characterized by pruritus, without rash, with raised serum transaminases and bile acids. It is more common in women who also develop pre-eclampsia. The condition is not thought to be more common in women infected with HIV but the finding of raised transaminases can be confused with the hepatic effects of antiretroviral drugs. OC is associated with maternal liver impairment and foetal morbidity and mortality and positive diagnosis is therefore important.

It may be difficult to distinguish the toxic effect of antiretrovirals from certain medical disorders of pregnancy, such as pre-eclampsia, HELLP (Haemolysis, Elevated Liver enzymes and Low Platelets) syndrome, obstetric cholestasis and acute fatty liver of pregnancy. If these disorders are suspected, additional tests should be undertaken for lactic acidosis, hepatitis and pancreatitis. If there is lactic acidosis (>5 mmol/L) consideration should be given to interrupting therapy. Monitor lactic acidemia (2–4.9 mmol/L) carefully. This is most commonly seen in patients taking didanosine or stavudine. The presenting symptoms of lactic acidosis may be nonspecific, but may include gastrointestinal disturbance, fatigue, fever and breathlessness. Close

collaboration between the HIV physician and obstetrician is mandatory for any woman who becomes acutely unwell in pregnancy to avoid diagnostic pitfalls.

In the unlikely event of a maternal death, a post-mortem should be conducted by a pathologist with experience in maternal death and HIV disease. In the event of a coroner's post-mortem the report should be obtained for audit.

13.3.3 Antepartum haemorrhage

Conditions associated with vaginal bleeding in pregnancy, such as placenta praevia and placental abruption, may increase the risk of mother-to-child transmission. There is no published evidence that helps decision-making regarding delivery, but in general the risks to the mother of delivery or continued blood loss, as well as the risks to the foetus of continued blood loss, must be weighed against the risks of mother-to-child transmission and prematurity.

13.3.4 Pre-term labour

The association between ART and risk of pre-term labour is discussed in Section 11.

PTD has been identified as a risk for HIV mother-to-child transmission [205,206]. An HIV-positive woman presenting with threatened pre-term labour (intact membranes) should have a vaginal swab taken for bacteriology. At gestations <34 weeks, two doses of intramuscular betamethasone 12 mg 24 h apart should be administered in order to enhance foetal lung maturation. This management is no different from that of HIV-negative women. The use of tocolytic agents, which can be used to delay delivery for up to 48 h, will be determined by considering the risk of prematurity to the neonate compared with the risk of infection (see also Scenarios).

13.3.5 Pre-term pre-labour rupture of membranes at gestations > 34 weeks

PPROM is associated with 40% of pre-term deliveries and can result in significant neonatal morbidity and mortality. For the general population, in the absence of chorioamnionitis or foetal compromise, management is expectant and delivery is considered at 34 weeks. At this gestation, the small risk of severe neonatal morbidity and mortality associated with PTD is outweighed by the risk to both mother and neonate of chorioamnionitis.

For the HIV-positive woman, all the data on transmission in this setting are from the pre-HAART era where prolonged rupture of membranes and chorioamnionitis were associated with an increased risk of mother-to-child transmission [207]. Moreover, the woman may be more susceptible to overwhelming and life-threatening sepsis as a result of HIV-related immunosuppression [208–210]. In the absence of data to the contrary it is recommended that,

for a mother with HIV infection, PPRM after 34-week delivery of the baby should be expedited regardless of maternal viral load and therapy. Carefully search for genital infections, start erythromycin and have a low threshold for intravenous broad-spectrum antibiotics.

13.3.6 Pre-term pre-labour rupture of membranes at gestations < 34 weeks

When PPRM occurs before 34 weeks, consider the advisability of prolonging pregnancy in the light of maternal HAART, viraemia and the presence of any other pregnancy or HIV-related comorbidities. Start steroids immediately, carefully search for genital infections, start erythromycin and have a low threshold for intravenous broad-spectrum antibiotics. It may be possible to optimize the woman's HAART regimen to reduce the risk of mother-to-child transmission. Maternal single-dose NVP should be strongly considered, even in the presence of NVP-associated resistance, because of the highly efficient transplacental transfer and prolonged plasma concentrations in a neonate that may be unable to take oral PEP. Intravenous ZDV may be considered if the mother has detectable plasma viraemia. All maternal ART must be given regardless of any planned surgery.

Once two doses of steroids have been administered, elective delivery at < 34 weeks may be considered, balancing the risks of severe complications of prematurity and the availability of neonatal facilities with the risk of HIV infection, after multidisciplinary discussion involving the obstetricians, neonatologists and HIV physicians. There have been no randomized controlled trials to inform these decisions.

13.3.7 Term pre-labour rupture of membranes

The transmission risk for women with term PROM taking HAART who have undetectable plasma viraemia is unknown. A meta-analysis of studies conducted before use of HAART in pregnancy demonstrated a 2% incremental increase in transmission risk for every hour of ruptured membranes up to 24 h [211]. There is evidence of compartmentalization between the genital tract and plasma; genital tract HIV-1 has been detected in women with an undetectable plasma viral load [53,212]. It is therefore reasonable to assume that prolonged rupture of membranes, even in women with undetectable plasma viraemia, may be associated with an increased risk of mother-to-child transmission. Although this increased risk is likely to be small it seems prudent that delivery should be expedited. Broad-spectrum intravenous antibiotics (such as a cephalosporin and metronidazole) should be administered stat where there is evidence of chorioamnionitis and may be considered for all mothers planning a vaginal delivery. For those with a fully suppressed viral load and

favourable cervix and intending to deliver vaginally, induction of labour may be considered. Where PLCS was planned, HIV is still detectable or successful labour unlikely, early delivery by Caesarean section is recommended (see Scenario 7).

13.3.8 Prolonged pregnancy

The management of prolonged pregnancy is difficult in women infected with HIV. The current recommendation for the general pregnant population is that, provided that the mother and foetus are well, the foetus will benefit from delivery at beyond 41 weeks' gestation [213]. The risk of *in utero* foetal death (IUFD) at 41 weeks is estimated at 1 in 1000 and therefore induction of labour is usually recommended at this stage. Induction of labour is usually achieved using vaginal prostin or artificial rupture of the membranes (ARM) with the addition of a syntocinon infusion if contractions do not then start.

In the HIV-infected woman, it is generally held that early ARM may be associated with an increased risk of mother-to-child transmission, particularly if the maternal plasma viral load is detectable. This is because prolonged rupture of membranes is associated with an increased risk of mother-to-child transmission for women with detectable plasma viraemia and because early ARM where the membranes are tightly covering the foetal head may cause trauma to the foetal scalp, thereby increasing the risk of exposure to maternal blood and cervicovaginal secretions. The risk of sudden IUFD must therefore be weighed against both the risks of the method of induction described above and the increased rate of complications, including emergency Caesarean section, foetal distress, the need for epidural anaesthesia and assisted delivery. If the woman is keen to achieve a vaginal delivery, is on optimum HAART, has an undetectable viral load and favourable cervix then induction of labour may be considered, but it is generally recommended to perform a Caesarean section if spontaneous labour has not ensued prior to 41 weeks.

13.3.9 Vaginal birth after Caesarean (VBAC)

The general population are now recommended to attempt to deliver vaginally after previous Caesarean section in view of the high rates of successful vaginal delivery and the low risk of scar dehiscence [214]. The risk of dehiscence of a lower segment Caesarean scar in labour is of the order of 1 in 250. The probability of a successful vaginal delivery is dependent on current and past obstetric factors. In general, provided that the woman is being cared for in a consultant-led maternity unit and the labour properly monitored with rapid recourse to Caesarean section in the face of any difficulty, the outcome of trial of labour for mother and neonate is good, even if scar dehiscence occurs.

There are no data for women with HIV infection but prolonged exposure to maternal blood if dehiscence occurs might carry additional transmission risk. The usual criteria for elective vaginal delivery apply.

13.4 Management of delivery

13.4.1 Mode of delivery

A decision on mode of delivery should involve the mother, the obstetrician and the HIV physician in a detailed risk assessment. Discussion must take into account maternal plasma viral load, safety and efficacy data on mode of delivery by PLCS, including future pregnancy plans, the efficacy and toxicity of ART, and the wishes of the mother. Initial studies conducted prior to the use of HAART in pregnancy found a reduction in mother-to-child transmission with elective Caesarean section. A meta-analysis of 15 prospective cohort studies ($n = 8533$) [215] and a randomized controlled trial of mode of delivery in Europe ($n = 436$) [122] both supported the protective effect of elective Caesarean section, with reductions in mother-to-child transmission of 50 and 70%, respectively (Table 2).

Although maternal plasma viral load has an almost linear association with the risk of mother-to-child transmission [70], transmission has been reported when maternal viraemia was undetectable [75,216]. In a meta-analysis of seven prospective studies from the USA and Europe ($n = 1202$), of those with plasma HIV RNA <1000 copies/mL at or around delivery, the transmission rate for mothers taking ART was 1%, compared with 9.8% for those not taking therapy [74]. Caesarean section, either pre-labour or emergency, reduced the risk of mother-to-child transmission by two-thirds, independent of viral load or maternal ART. These data, collected when HIV RNA PCR assays were less sensitive than currently, suggest a protective effect of both ART and Caesarean section even at low maternal plasma viral loads [74]. Prospective data from the European Collaborative Study group ($n = 1983$) also suggested a reduction in transmission with elective Caesarean section for women with low plasma viraemia [134]. In this study of 4525 mother-child pairs recruited between 1997 and 2004, mother-to-child transmission from 1997 to 1998, at a time when only a small minority of pregnant women received HAART, was 5.06%. By 2001–2002, when the majority of women received HAART in pregnancy, mother-to-child transmission was 0.99%. However, among the 560 women with undetectable HIV RNA levels (44% with levels of <50 copies/mL), elective Caesarean section was associated with a 93% reduction in the risk of mother-to-child transmission compared with vaginal delivery or emergency Caesarean section (OR 0.07; CI 0.02–0.31; $P = 0.0004$).

Table 2 Evidence of the efficacy of pre-labour caesarean section (PLCS) to reduce the risk of mother-to-child transmission of HIV

	Transmission rate (%)		Odds ratio (95% CI)		Transmission rate (%)		Odds ratio (95% CI)	
	PLCS	SVD and other MOD	PLCS and ZDV*	SVD, other MOD and ZDV*	PLCS and advanced maternal disease**	SVD, other MOD and advanced maternal disease**	PLCS and advanced maternal disease**	SVD, other MOD and advanced maternal disease**
Meta-analysis, 15 cohorts pre-1997, USA and Europe, $N = 8533$ [215]	8.4 (72/857)	16.7 (1280/7676)	2 (4/196)	7.3 (92/1255)	13 (18/138)	21.4 (206/963)	0.13 (0.09–0.19)	Not given
European Mode of Delivery study	Allocated to PLCS	Allocated to SVD	Allocated to PLCS + ZDV*	Allocated to SVD + ZDV	Allocated to PLCS + CD4 <200 cells/ μ L	Allocated to SVD + CD4 <200 cells/ μ L		
ELCS at 38 weeks, [122]	1.8 (3/170)	10.5 (21/200)	0.8 (1/119)	4.3 (5/117)	0 (0/16)	14.3 (2/14)		NS
1983–1998, $N = 436$	Actual CS (ELCS + EMCS)	Actual SVD	Actual CS + ZDV (ELCS + EMCS)	Actual SVD + ZDV	Actual CS + CD4 (ELCS + EMCS)	Actual SVD + CD4 <200 cells/ μ L		
	3.4 (7/203)	10.2 (17/167)	2.1 (3/144)	3.3 (3/92)	0 (0/20)	20 (2/10)		NS

*Full 076 protocol with antepartum, intrapartum, and postpartum ZDV.

**Advanced maternal disease – an AIDS diagnosis and/or CD4 <200 cells/mL or <14%. CI, confidence interval; CS, Caesarean section; ELCS, elective Caesarean section; EMCS, emergency Caesarean section; MOD, mode of delivery; NS, not significant by Fisher's exact test; PLCS, pre-labour Caesarean section; SVD, spontaneous vaginal delivery; ZDV, zidovudine.

In the current era of HAART, it is unclear whether PLCS provides additional benefit if maternal plasma viraemia is undetectable (<50 copies/mL plasma). Data from the UK and Ireland (1990–2004) showed a significantly lower mother-to-child transmission rate in women on HAART who undergo a PLCS (0.7%) compared with women who deliver vaginally (1.9%). The analysis included unplanned as well as planned vaginal deliveries, and was not restricted to women who achieved undetectable viral load [3]. In the French Cohort, PLCS did not significantly reduce the rate of transmission compared with vaginal delivery if maternal viral load was <400 copies/mL [123]. In the UK and Ireland cohort (2000–2006), 2117 infants were born to women with an HIV viral load <50 copies/mL plasma on HAART. There were three infections (0.1%), two in infants born by PLCS and one in an infant born by planned vaginal delivery [4]. These data support the strategy of offering HIV-positive women with uncomplicated pregnancies, on HAART with no detectable viraemia, the option of a trial of labour.

13.4.2 Management of Caesarean section

The timing of pre-labour pre-rupture of membrane Caesarean section is a balance between the likelihood of transient tachypnoea of the newborn (TTN) and the risks of labour supervening before the scheduled Caesarean section. The general pregnant population is now advised that elective Caesarean section should be performed at 39 weeks when the frequency of TTN is 1 in 300 [217]. The risk of TTN doubles for every week earlier that delivery occurs. The risks of membrane rupture and labour increase as the pregnancy progresses towards term. Therefore, where the mother is on optimal HAART and the viral load is undetectable, and there are no other reasons for recommending a Caesarean section, it may be reasonable to defer this until 39 weeks. Where there is a detectable viral load or any clinical reason to suppose that the woman will labour early, then earlier Caesarean section will be wise and is usually scheduled at 38 weeks' gestation.

If indicated, the ZDV infusion should start 4 h before the start of the Caesarean section and continue until the umbilical cord has been clamped.

Although there was a suggestion a number of years ago that the so-called 'bloodless Caesarean section' might confer some protection on the foetus [218] there has been no further evidence to substantiate this. However, it would seem to be good practice to keep the surgical field relatively haemostatic and not to rupture the membranes until the head is delivered through the surgical incision, if possible. The cord should be clamped early.

Several studies have suggested that the complications of Caesarean section are higher in women with HIV, with the

highest risks in women undergoing emergency Caesarean section. The most frequent reported complication was postpartum fever and this was increased in women with low CD4 cell counts [219,220]. However, many of these studies were performed prior to the recommendation that prophylactic antibiotics should be administered intra-operatively to all women undergoing Caesarean section to reduce infectious morbidity. A more recent case-controlled study from the UK, where all HIV-positive women received ART and prophylactic antibiotics ($n = 44$), did not demonstrate any differences in post-operative morbidity [221]. This is consistent with data from a Dutch cohort ($n = 143$) [167] and studies from Latin America and the Caribbean, which also showed low rates of postpartum morbidity [222]. However, the observation that HIV-infected women may be at increased risk of postpartum morbidity, regardless of mode of delivery, was suggested by a case-control study of women delivering in 13 European centres that found a higher rate of morbidity in HIV-infected women ($n = 408$) when compared with non-HIV-infected women [220]. HIV-infected women may not, therefore, be suitable for early discharge in the postpartum period.

13.4.3 Management of vaginal delivery

When vaginal delivery is planned, spontaneous onset of labour is preferable to induction (see 'Prolonged pregnancy' for considerations around induction of labour). Because of the association of mother-to-child transmission with the duration of membrane rupture, labour must progress normally and the mother and the foetus should be in good condition throughout. Foetal blood sampling and foetal scalp electrodes are contraindicated. Because of the necessity to avoid invasive procedures in the foetus, there should be a low threshold for Caesarean section in the face of slow or difficult labour or concern about foetal condition. Amniotomy should be avoided unless there is slowing of progress of second-stage labour. In this situation the risk of trauma of the foetal scalp is likely to be very small, and there is unlikely to be a lengthy delay between amniotomy and delivery.

If instrumental delivery is required, low-cavity traction forceps are the instrument of choice as it is generally accepted that they are associated with lower rates of foetal trauma than ventouse. Mid-cavity and rotational deliveries should be avoided.

13.5 Postpartum care

13.5.1 Suppression of lactation

Cabergoline 1 mg orally stat within 24 h of birth will assist with suppression of breast-milk production.

13.5.2 Contraception

The importance of contraception should be emphasized, particularly as women will not be breastfeeding. The BHIVA guidelines on the management of sexual and reproductive health of people living with HIV infection (2007) are found at www.bhiva.org/cms1191550.asp.

14.0 Pregnancy in women with HIV-2 infection

First described in 1986, HIV-2 is found mainly in West Africa, the epicentre of the epidemic being Guinea Bissau, where a prevalence of up to 10% has been reported [223], and some areas of Southern India. In Europe, HIV-2 is found in regions with a historical relationship with West Africa, in particular Portugal and France. Although in Europe the number of people with HIV-2 infection is small it is gradually increasing as global migration influences population dynamics. In the UK approximately 130 infections with HIV-2 have been reported to the Health Protection Agency (B. Rice, HPA, personal communication). Although HIV-1 and HIV-2 are related, there are important differences between them that influence pathogenicity, natural history and therapy.

HIV-2 appears to be less readily transmitted than HIV-1 both sexually [224,225] and from mother to child [226–228]. HIV-2 appears to have a less aggressive natural history than HIV-1 [229,230]. In general the viral load in HIV-2 is lower than that in HIV-1, and high CD4 cell counts are associated with low levels of viral replication [231]. High levels of viral replication, however, are correlated with poor prognosis and are an indication to initiate therapy [232,233].

There is little clinical evidence on which to base treatment strategies for patients with HIV-2. HIV-2 differs from HIV-1 in its susceptibility to ART and also follows different mutation pathways to develop drug resistance. These factors mean that selection of, and adherence to, the first antiretroviral combination regimen, already crucial for successful treatment of HIV-1 infection, is that much more critical for HIV-2 [234] (see Table 3).

NNRTIs have no activity against HIV-2, with the 50% inhibitory concentration (IC₅₀) being over 100-fold greater than that for HIV-1 [235]. Amongst the NRTIs there is a suggestion that ZDV may have less activity against HIV-2 than HIV-1, although this is based so far only on *in vitro* data [236]. A variety of polymorphisms exist in the HIV-2 protease gene at positions that in HIV-1 are associated with reduced drug susceptibility [237]. *In vitro* phenotypic analysis of HIV-2 isolates has shown reduced susceptibility to amprenavir, atazanavir and tipranavir but little difference for lopinavir when compared with HIV-1 [238]. A

Table 3 Expected utility of licensed antiretroviral drugs for HIV-2 (modified from Parkin and Schapiro [310])

Drug	Consider for treatment of HIV-2	Comments
NRTI	NOT AS MONO or DUAL THERAPY	
Abacavir	Yes	
Didanosine	Use with caution	Low-level innate resistance in SIV and some HIV-2?
Emtricitabine	Yes	Based on similar resistance profile to lamivudine
Lamivudine	Yes	
Stavudine	Use with caution	
Tenofovir	Yes	Only NRTI active against Q151M-containing virus
Zalcitabine	Use with caution	Low potency
Zidovudine	Yes	Not as monotherapy. Expect Q151M after failure
NNRTI		
Efavirenz	No	Innate resistance
Nevirapine	No	Innate resistance
Protease inhibitors		
Fosamprenavir, amprenavir	No	May be active in combination with low-dose ritonavir
Atazanavir	No	Inactive <i>in vitro</i> against HIV-2 (with ritonavir)
Indinavir	Yes	(with ritonavir)
Lopinavir	Yes	(with ritonavir)
Nelfinavir	No	Low-level resistance; poor clinical response
Ritonavir	Yes/No	Use with caution. Low-level resistance; low potency
Saquinavir	Yes	
Tipranavir	Yes	
Darunavir	Yes	
Fusion inhibitors		
Enfuvirtide	No	Innate resistance susceptibility threshold not defined

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; SIV, simian immunodeficiency virus.

poor clinical response has been demonstrated to nelfinavir [239].

Enfuvirtide is not effective against HIV-2 [234].

In some circumstances patterns of resistance in HIV-2 that emerge under drug pressure may be the same as those seen in HIV-1 [240]. However, there are significant differences, particularly in NRTI pathways. The multiple resistance NRTI mutation Q151M has been noted to occur with increased frequency in HIV-2 in response to NRTI therapy [241–243]. The pathways by which NRTI resistance occurs in HIV-2 may differ from those of HIV-1 and resistance may develop more rapidly because of other pre-existing mutations [244].

Pregnant women with detectable HIV-2 should be managed using a HAART regimen to which the virus is sensitive.

In the light of the current, albeit limited, data on NRTI resistance pathways, ZDV monotherapy should not be used in women with HIV-2. If the mother has a high CD4 cell

count (>500 cells/ μ L) and a consistently undetectable HIV-2 viral load, drug therapy may not be indicated and the possible risks and benefits of this approach should be discussed with the mother.

The risk to the baby from breast milk is probably lower than for HIV-1 but it is advisable to avoid this method of feeding.

Infants born to infected women should ideally be monitored for HIV-2 proviral DNA and samples should be referred to a specialist laboratory. Determining loss of HIV-2 antibodies by 18 months of age is also recommended.

14.1 Mode of delivery

If the CD4 lymphocyte count is >500 cells/ μ L and the untreated HIV-2 viral load is below the limit of detection (BLD), consider spontaneous vaginal delivery. Similarly, if the viral load is BLD on HAART, consider spontaneous vaginal delivery. If the viral load is not BLD or CD4 is <500 cells/mL, plan for PLCS at 38 weeks.

14.2 Laboratory investigation and monitoring for HIV-2 in pregnancy

Making the correct diagnosis is crucial as therapy will differ significantly if HIV-2 is present. Not all laboratories differentiate between HIV-1 and HIV-2, so it is important that any patient who may have been at risk of HIV-2 has the appropriate investigations performed.

14.2.1 *At the time of writing in the UK HIV-2 viral load assays are only carried out by:*

Prof. Deenan Pillay/Dr Bridget Fern
Department of Virology, Royal Free & University College London Medical School, Windeyer Bldg, 46 Cleveland St, London W1T 4JF, UK
Tel: 0207 6799490/9483; fax: 0207 5805896;
email: d.pillay@ucl.ac.uk

14.2.2 *HIV-2 genotyping can be performed by:*

Dr Erasmus Smit, Consultant Virologist
West Midlands Public Health Laboratory, Health Protection Agency, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK
Tel: 0121 424 1239; fax: 0121 772 6229;
email: erasmus.smit@heartofengland.nhs.uk

The UK HIV-2 reference laboratory is based at the HPA in Colindale and is led by:

Ms Jennifer Tosswill
Health Protection Agency, Sexually Transmitted and Blood Borne Virus Laboratory, 61 Colindale Avenue, London NW9 5HT, UK

Tel: 020 8327 6274; email: jennifer.tosswill@hpa.org.uk

The laboratories should be contacted in advance of sending specimens to discuss appropriate samples and the conditions for transporting them.

15.0 HIV and hepatitis B and C coinfections

15.1 Mother-to-child transmission of hepatitis C virus

All women with HIV should be screened for both hepatitis B and C infection. Women with very low CD4 cell counts may not produce a serological response to HCV and molecular assays to detect HCV RNA may be considered in this circumstance.

In women who are infected with HCV there is a low rate of transmission of HCV from mother to infant and current estimates indicate that up to 6% of women will infect their child [245–247]. The timing and route of transmission are unclear and it is not known whether transmission is transplacental or during delivery. HCV plasma viral load is associated with transmission; women with undetectable viraemia are highly unlikely to transmit. HCV viraemic mothers (HCV-positive, HIV-negative) have an increased transmission rate of up to 10% [246,248]. Some studies indicate that instrumental delivery may be associated with an increased rate of transmission and one study suggests that delivery by Caesarean section may reduce the rate of transmission [245,249]. These data arise from relatively small-scale, retrospective studies and the findings have not been confirmed. Breastfeeding is not thought to increase the risk of infection [245,247,249–251].

In women who are HCV and HIV coinfecting, transmission is increased to up to 15%, with higher rates in those who are HCV viraemic [246,247,250,252]. Pappalardo's meta-analysis shows an increased OR for HCV transmission of 2.82 (95% CI 1.78–4.45) if the mother is coinfecting with HIV [253]. Effective control of HIV is associated with a reduction in the rate of HCV transmission, although the mechanisms of this improvement are unclear [254,255]. No studies to assess the benefits of surgical, rather than vaginal, delivery have been performed in HIV/HCV coinfecting women. In view of the reduced mother-to-child transmission of HCV with elective Caesarean in HIV-negative women, and the reduced mother-to-child transmission of HCV with effective control of HIV, it would seem prudent to recommend HAART and consider PLCS for all HIV and HCV coinfecting mothers.

Guidelines on the management of adults with HIV/HCV coinfection *per se* can be obtained from the BHIVA website (www.bhiva.org/cms119156.asp).

15.2 Diagnosis of hepatitis C virus infection in children

In view of the increased risk of HCV infection in children born to women who are coinfecting with HIV, testing for HCV is recommended for all infants born to dually infected mothers. The optimal timing and nature of the test that should be used are unclear. However, transmission of maternal antibodies is almost invariable and therefore antibody testing is unreliable until the infant is 15–18 months old. Testing for viraemia during the first few months of life may not reliably identify chronically infected children and some studies suggest that a proportion of infants who are originally HCV RNA positive will clear virus without intervention [245,249]. To identify chronically infected children repeat PCR testing for HCV RNA should be performed during the first year of life. A proportion of infected children do become HCV RNA negative, so both serological and molecular tests are important [256,257].

15.3 Mother-to-child transmission of hepatitis B virus

Maternal infection with HBV is associated with a high incidence of transmission of HBV to their infants. Transmission can be effectively prevented by immunization of the at-risk infant shortly after birth [256] and materno-foetal transmission of HBV has been greatly reduced in developed countries by effective vaccination programmes. Materno-foetal transmission of HBV is related to the level of HBV viraemia. In general, women who are HBeAg positive have a high incidence of transmission of HBV to their infants (90%) and the risk is reduced in women who are HBeAg negative (40%) [258]. However, women who are HBeAg negative with a high level of HBV viraemia may have an increased incidence of materno-foetal transmission, although the magnitude of the increased risk and the precise level of viraemia at which the risk becomes significant are not known. HBV DNA quantification is therefore recommended for all HBsAg-positive mothers. A Chinese study demonstrated a reduction in vertical HBV transmission where mothers received either 3TC or hyperimmune globulin, compared with no treatment [259]. Further studies to define the optimal treatment of maternal disease as well as to prevent transmission are required.

HIV may increase the serum HBV DNA levels and it is plausible that coinfection will increase the rate of HBV transmission, but this has not been shown. A small study from Tanzania suggested that coinfection did not increase the risk of transmission but an increase in the rate of transmission could not be excluded [260].

In pregnant women with HIV/HBV coinfection it is recommended to use a HAART regimen that includes

agents active against both HBV and HIV. Lamivudine, emtricitabine and tenofovir are active against both HBV and HIV. As there has been most experience with the use of 3TC in pregnancy, HIV and HBV coinfecting mothers should probably be treated using a regimen containing tenofovir and 3TC plus a third agent. Guidelines on the management of adults with HIV/HBV coinfection *per se* can be obtained from the BHIVA website (www.bhiva.org).

15.4 Diagnosis of hepatitis B virus infection in children

Infants born to HBV-positive mothers in the UK should receive active HBV vaccination at birth and at 1, 2 and 12 months of age. Infants born to mothers with a high risk of infectivity should also receive HBIG at birth (no national consensus: consult local hospital policy). At 15–18 months of age, infants should be screened for HBsAg to confirm that they have not been infected and for HBV surface antibody (HBsAb) to confirm that they have responded to their vaccination.

It is standard practice in the UK to offer active vaccination to all infants born to HBsAg-positive mothers and to offer passive vaccination with HBIG to children born to mothers who are HBeAg positive.

16.0 Management of infants born to HIV-infected mothers

(See Tables 4 and 5 for quick reference guides to infant antiretroviral regimens and infant dosing.) Most neonates born in the UK to mothers known to have HIV will be exposed to ART *in utero*, during delivery, and after birth for the first 4 weeks of life. The range of different combinations of ART to which neonates are being exposed is constantly increasing. Neonatal drug metabolism is generally slower than that of older infants or children, and premature neonates have even less efficient metabolism [261]. Neonatal dosing regimens have been developed for most of the NRTIs, for the NNRTI NVP, and for the PI nelfinavir (Table 5) although the latter is currently not available in Europe (November 2007). Studies of dosing regimens for other drugs (e.g. lopinavir/ritonavir and tenofovir) are in process. Adequate neonatal blood levels are difficult to achieve with nelfinavir and there is little experience of other PIs. A recent population pharmacokinetic study of ritonavir-boosted lopinavir including six neonates suggested that on standard doses (300 mg/m² bid) neonatal trough levels on twice-daily dosing may be too low [262–265]. Where ritonavir-boosted lopinavir liquid is required for neonatal PEP, consideration should be given to a tid regime (300 mg/m² tid) and therapeutic drug monitoring should where possible be undertaken (further

Table 4 Antiretroviral studies in infants with doses and combinations

Drug	Dose	Mono/combo	Study	New dose	Comments/Side effects
Zidovudine (ZDV/ZDV) (Retrovir)	Oral	Combo (+ 3TC)	Moodley 2001 [311]		Anaemia, neutropaenia, more common with combination therapy in mother and infant. In French study of ZDV + 3TC small proportion of infants either required transfusions or early stop of therapy. ZDV and d4T should not be administered together in view of theoretical risk of negative interaction
	Term (> 34 weeks) 4 mg/kg bid	Mono	Boucher 1993 [268]	*New	
	2 mg/kg qid	Mono	Capparelli 2003 [269]	*New	
	Prem (30–34 weeks) 2 mg/kg bid for 2 weeks then 2 mg/kg tid for 2 weeks.	Mono	Capparelli 2003 [269]	*New	
	Prem (<30 weeks) 2 mg/kg bid for 4 weeks	Mono	Boucher 1993 [268]		
	Intravenous				
Term 1.5 mg/kg qid					
Prem 1.5 mg/kg bid					
Lamivudine (3TC) (EpiVir)	2 mg/kg bid	Combo (all with ZDV)	Moodley 2001 [311] Mandelbrot 2001 [109] Moodley 2003 [125]		Anaemia, neutropaenia (but less common than with ZDV), more common with combination therapy in mother and infant
Didanosine (ddl) (Videx)	60 mg/m ² bid 100 mg/m ² qd	Mono Combo (with d4T + NEL)	Wang <i>et al.</i> 1999 [312] Rongkavilit 2001 [313]	*New *New	Difficult to separate dosing from feeding, and ddl much better absorbed on an empty stomach. May cause GI symptoms. Variable absorption in neonate
Stavudine (d4T) (Zerit)	1 mg/kg bid	Combo (with ddl + NEL)	Rongkavilit 2001 [313]		ZDV and d4T should not be administered together in view of theoretical risk of negative interaction
Abacavir (ABC) (Ziagen)	2 mg/kg bid	Mono	Johnson 2000 [314]		Hypersensitivity reaction not been noted in infants (only small numbers treated)
Nevirapine (NVP/NEV) (Viramune)	Daily dosing regime	Mono	Shetty JAclmmDsynd 2003 [266]	*New	Daily dosing regime from HIVNET 023 (breastfeeding prophylaxis study)
	200 mg to mother in labour, then 2 mg/kg qd for 1st week, then 4 mg/kg qd for 2nd week (see Table 5)	Mono			
Nefinavir (NEL/NFV) (Viracept) NB: no longer available	Single-dose regime		Guay 1999 [100]		Single-dose regime should be avoided as high risk of development of resistance in mother and infant
	200 mg to mother in labour, then one 2 mg/kg dose at 48–72 hrs from birth				
Nefinavir (NEL/NFV) (Viracept) NB: no longer available	50–75 mg/kg bid	Combo (with ZDV + 3TC)	NICHD/HPTN 040/P1043	*New	Ongoing RCT of different regimes for PEP for infants born to mothers with antenatally untreated HIV
	15/30/45 mg/kg bid	Combo (with ddl + d4T)	Bryson 2000 [264]		
	90 mg/kg/day (total dose)	Combo (with ddl + d4T)	Rongkavilit 2002 [263] Faye 2002 [265]		
Lopinavir/ritonavir (Kaletra)	300 mg/m ² bid	Combo	Jullien, 2006 [262]		This preliminary PK study has suggested that this may give low levels in neonates, further studies are underway.
Co-trimoxazole (septrin)	900 mg/m ² qd Mon/Wed/Fri < 6 months 120 mg qd Mon/Wed/Fri 6–12 months 240 mg qd Mon/Wed/Fri	PCP prophylaxis	Simmonds 1995 [315]		May cause rash, bone marrow suppression. Give to infants born to mothers with a higher risk of transmission

*Change of dose from previous British HIV Association (BHIVA) guidelines.

bid, twice daily; tid, three times a day; qd, once daily; GI, gastrointestinal; HIVNET, HIV Network for Prevention Trials; NICHD/HPTN, National Institute of Child Health and Human Development/HIV Prevention Trials Network; PCP, *Pneumocystis carinii* pneumonia; PENTA, Paediatric European Network for Treatment of AIDS; PEP, post-exposure prophylaxis; PK, pharmacokinetics; Prem, premature; RCT, randomized controlled trial.

studies are underway). See the Children's HIV Association website for dosing updates (www.chiva.org.uk).

In contrast to the PIs, NVP efficiently crosses the placenta and is well absorbed by the neonate [266,267]. Neonatal metabolism of NVP is induced where there has been antenatal *in utero* exposure [186,187]; if this drug is given to the neonate, when the mother has taken it for 3 (or more) days, the full dose of 4 mg/kg/day should be started at birth, rather than the induction dose of 2 mg/kg/day (Table 4).

Because of the long half-life of NVP, when used in combination therapy for the infant, NVP should be stopped 2 weeks before the other drugs to reduce the risk of monotherapy exposure and development of NNRTI resistance [185].

The only ART available for intravenous (i.v.) use in sick and/or premature neonates, unable to take oral medication, is ZDV [268,269]. Reduced oral and i.v. dosing schedules for premature infants have only been developed for ZDV (Tables 4 and 5) [269].

Table 5 Suggested treatment for newborn infants as post-exposure prophylaxis (PEP) for HIV (all treatment is for 4 weeks)

Scenario	Infant treatment	Comments/suggested doses
Mother on ZDV monotherapy + PLCS + i.v. ZDV in labour	ZDV monotherapy	Well term infant, ZDV 4 mg/kg bid (see Table 4 for prem/sick infant doses)
Mother on HAART, viral load <50 copies/mL; HAART contains ZDV	ZDV monotherapy	Well term infant, ZDV 4 mg/kg bid (see Table 4 for prem/sick infant doses)
History of ZDV resistance	Use the NRTI with most experience in mother's regime: 3TC>d4T>ABC>ddl	3TC 2 mg/kg bid; d4T 1 mg/kg bid; ABC 2 mg/kg bid; ddl 100 mg/m ² qd. If possible, avoid ddl because of feeding restriction
Mother presents with viral load >50 copies/mL and no previous ART exposure (e.g. premature labour/ROM; presentation at term with no ART)	Combination therapy ZDV + 3TC + NVP	Well term infant, ZDV 4 mg/kg bid (see Table 4 for prem/sick infant doses) + 3TC 2 mg/kg bid + NVP 2 mg/kg qd 1st week and NVP 4 mg/kg qd 2nd week (use NVP 4 mg/kg qd for 2 weeks if the mother has received >3 days NVP). Stop NVP after 2 weeks, in view of long half-life. Continue other NRTIs for full 4 weeks
Mother presents with viral load >50 copies/mL and previous ART exposure (e.g. premature labour/ROM; presentation at term)	Combination therapy Seek expert advice	Will need to tailor therapy according to maternal resistance pattern/ART exposure
Maternal HIV diagnosis ascertained after delivery (no previous ART)	Combination therapy ZDV + 3TC + NVP, start as soon as possible after delivery, but if presents after 48–72 hours may be too late for PEP, unless mother is breastfeeding.	Well term infant, ZDV 4 mg/kg bid (see Table 4 for prem/sick infant doses) + 3TC 2 mg/kg bid + NVP 2 mg/kg qd 1st week and NVP 4 mg/kg qd 2nd week (use NVP 4 mg/kg qd for 2 weeks if the mother has received >3 days NVP). Stop NVP after 2 weeks, in view of long half-life. Continue other NRTIs for full 4 weeks
Premature or unlikely to tolerate oral feeds	ZDV monotherapy i.v.	Switch to oral when tolerating feeds
Maternal viral load <50 copies/mL	Add maternal NVP (at least 2 hours prior to delivery if possible)	
Maternal viral load >50 copies/mL or unknown		

ABC, abacavir; ART, antiretroviral therapy; bid, twice daily; d4T, stavudine; ddl, didanosine; HAART, highly active antiretroviral therapy; i.v., intravenous; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PEP, post-exposure prophylaxis; PLCS, pre-labour Caesarean section; prem, premature; qd, once daily; ROM, rupture of membranes; 3TC, lamivudine; ZDV, zidovudine.

16.1 When to use monotherapy for the infant as post-exposure prophylaxis

Where a low-transmission-risk mother chooses ZDV monotherapy with Caesarean section delivery, the infant should also receive ZDV monotherapy.

Where a mother on combination therapy delivers with a viral load of <50 copies/mL, current practice is to use single-drug therapy for the neonate, as this is practically easier for the family and may reduce the incidence of adverse events in the neonate. The drug chosen from the maternal combination is usually the NRTI with the best-known infant pharmacokinetics (ZDV, 3TC, etc). With infant feeding patterns, it is difficult to separate drug dosing from feeds, so drugs without food restrictions are preferred and didanosine is avoided. ZDV should not be given to an infant born to a mother who is receiving stavudine because of the theoretical negative competitive interaction. Monotherapy with NVP given to either mother or infant should be avoided because of the high rate of development of resistance even with a single dose given to mother and/or infant, as discussed previously [101].

16.2 When to use combination antiretroviral therapy for the infant as post-exposure prophylaxis

With regard to prevention of mother-to-child transmission of HIV, there have been very few studies of combination therapy in neonates and no published studies regarding the efficacy of triple combinations. Dual combination ART given to the neonate (ZDV plus 3TC *vs.* ZDV) had additional benefit over single-drug treatment (in historical controls) in terms of reduction of transmission when mothers were also receiving dual ART [109]. A randomized African study that compared short-course (1 week) treatment of the infant with either ZDV plus NVP or NVP also demonstrated the superiority of two drugs [270]. However, in the randomized African SAINT study, no significant difference in transmission rate was demonstrated in short-course treatment with either ZDV plus 3TC or NVP after perinatal treatment of the mother [125].

There are three situations where triple combination PEP for neonates is advisable.

1. Post-delivery prophylaxis: where the mother is found to be HIV-infected only after delivery.

2. Unplanned delivery: for example, prematurely prior to starting ART, or after a late presentation when details of maternal HIV parameters may not be available.
3. Persistent maternal viraemia on HAART: for example, because of poor adherence or viral rebound with resistance.

Two studies have examined the first situation where, because of late diagnosis of the mother, treatment could only be given to the infant after birth. In a US cohort study a reduced risk of transmission, compared with no intervention, was observed in infants commenced on ZDV monotherapy provided that this was started within 48 h of birth [119]. In a randomized African study of after-birth prophylaxis, babies born to mothers presenting at delivery received either single-dose NVP or single-dose NVP plus a week of ZDV [270]. Of the babies who were HIV negative on testing at birth, 34 (7.7%) who received NVP plus ZDV and 51 (12.1%) who received NVP alone were subsequently infected ($P = 0.03$) – a protective efficacy of 36% for the dual combination.

There have been no randomized studies of combination infant treatment after emergency delivery. Despite this, it is logical to consider it appropriate for neonates, as it is standard of care for any other PEP cases, where the level of blood/body fluid exposure is likely to be much lower.

For infants born to ART-naïve women, ZDV, 3TC and NVP is the combination therapy regimen with most experience. Infants born to treatment-experienced mothers may require other combinations, especially if there is a possibility of ART resistance (seek expert advice).

Resistance testing should be carried out in the mother in such a situation, although this will only give information in retrospect, and choice of treatment will have to be made on a best-guess basis with the history of drug exposure and any previous resistance data on the mother. If the infant is found to be infected, then the first HIV-positive sample should also be tested for the resistance pattern of the transmitted virus.

16.3 Treating premature infants: loading the infant with antiretroviral therapy before birth

Although premature infants are at most risk of HIV infection they are also the most difficult to treat with PEP. Most infants born at <30–32 weeks gestation will not be able to feed orally for the first few days, with the only licensed i.v. treatment available to them being ZDV. Therefore, where possible, the infant should be loaded with ART before delivery, via the maternal circulation

across the placenta. Most PIs do not cross the placenta in significant concentrations and NRTIs have concentrations of 60–100% in cord blood, so mothers should always continue their medication right up until delivery. A single dose of NVP given to the mother at least 2 h before delivery will be present in the infant circulation for up to 7 days [271]. Tenofovir may also have a prolonged half-life in the neonate, and this is under investigation.

Even if the mother is receiving a PI-based regimen, a single additional dose of NVP may be given to load the foetal circulation; thus the neonate will receive at least ZDV and NVP for the first 5–7 days of life. In the NVP-naïve mother, to prevent development of resistance, the maternal washout period of NVP should be covered with an appropriate 'tail' of ART.

The premature neonate is at risk of necrotizing enterocolitis if oral feeding is commenced too soon or increased too rapidly. Whether very early oral administration of antiretrovirals can exacerbate this is not known, but in general oral drugs should only be given along with the establishment of oral feeds [272]. Once the infant is successfully oral feeding, i.v. ZDV should be changed to oral.

16.4 When to start and duration of antiretroviral treatment for neonates

Neonatal PEP should be commenced as soon as possible after birth, certainly within 4 hours, and this is particularly important where the mother has not received any ART. In the PACTG 076 study ZDV was administered for 6 weeks after birth and this subsequently became standard of care [114]. However, in a Thai study, where a short course of 3 days of neonatal treatment was compared with 6 weeks, there was no increased transmission where the mother received ZDV from 28 weeks' gestation [115]. In the UK, neonates are treated for 4 weeks in line with PEP guidelines in other situations [273].

16.5 Side effects of treatment

16.5.1 Long term

Long-term side effects of perinatal exposure to ART can be considered in four main categories: teratogenic; carcinogenic; developmental; and mitochondrial. However, there may be others not yet recognized [274]. Teratogenicity is most likely to be a problem with first trimester exposure to ART + / – other drugs. All currently licensed antiretroviral therapies (except efavirenz, which has recently been reclassified D) are classified either B or C for use in pregnancy by the Food and Drug Administration (FDA). All women who receive ART in pregnancy should be registered anonymously and prospectively with the Antiretroviral Pregnancy Registry (www.apregistry.com), which

is updated twice a year. To date, a slight increase in overall congenital abnormalities above the background rate has only been reported for didanosine; however, no specific foetal abnormalities have been identified with this or any other drugs (see Section 11). Detailed foetal anomaly scanning around 21 weeks is advised after first trimester exposure to any combination of ART. NRTI exposure could theoretically lead to a long-term risk of carcinogenicity, although no increased rate has yet been identified [275]. So far, no adverse growth or developmental effects of ART exposure have been demonstrated in children [276,277]. Mitochondrial toxicity after perinatal ART exposure, with two deaths from encephalopathy, was first reported in uninfected infants from the prospectively followed French cohort [278]. Deaths have not been identified in other large cohorts [279–282]. However, laboratory analysis of mitochondrial DNA has demonstrated abnormalities in infants born to ART-treated mothers and this is an area of ongoing investigation [283]. In the long-term follow-up of the infants from the 076 study, two ZDV-exposed children were shown to have unexplained retinopathy and cardiomyopathy, which could potentially be related to mitochondrial dysfunction [277]. A long-term follow-up study of health and development in about 700 ART-exposed children to 3–5 years of age, via annual parental questionnaire, in the UK did not demonstrate any specific health problems [284,285]. However, although parents were generally supportive of continuing follow-up for these children [285], in practice this was difficult and incomplete because of family mobility, concerns about confidentiality, and poor attendance for follow-up appointments.

In a separate initiative, data on infected and uninfected infants reported to the National Study of HIV in Pregnancy and Childhood (NSHPC) are linked to routinely collected Office for National Statistics (ONS, www.statistics.gov.uk) data, a process known as ‘flagging’. A cancer or death registration for any of these children will be reported back to the NSHPC and linked with information on prenatal exposure. Ninety-five per cent of HIV-exposed infants born in 2001–2004 in England or Wales had been flagged by the end of 2005, and at that time no cancers had been notified [286].

16.5.2 Short term

Short-term acute mitochondrial toxicity may rarely present in the newborn period, exacerbating the metabolic stress of delivery. A small number of sick infants have been reported with severe lactic acidosis, multisystem failure and anaemia, not attributable to any other cause; all have recovered with supportive care [287]. Elevated lactic acid levels have also been found in asymptomatic ART-exposed infants [288]. Neonatal anaemia and neutropenia have

been reported in infants exposed to NRTIs; these may be worse where there is exposure to combination therapy, or more prolonged treatment [109]. Transfusion is rarely required and most children appear to respond to discontinuation of marrow suppressive therapy. However, a more recent study of over 4000 infants from the French cohort has demonstrated that perinatal ZDV may exert a small but significant and durable negative effect on haematopoiesis up to the age of 18 months [289]. The mechanism and longer term significance of this bone marrow suppression are not known. An increased rate of febrile seizures in ART-exposed infants has also been reported from the French perinatal cohort [290]. Whether different combinations of ART may be more or less deleterious to the neonate is not known.

In view of the potential metabolic abnormalities reported with ART, neonates exposed to ART should have baseline blood tests, including full blood count (FBC), glucose, urea and electrolytes (U + E) and LFTs; as well as diagnostic HIV PCR tests. For those exposed to atazanavir, bilirubin levels should be checked. It is our practice to repeat these tests with each set of HIV diagnostic samples. Lactate and pH monitoring for mitochondrial toxicity should be undertaken in any symptomatic newborn but does not appear to be necessary in otherwise well infants.

16.6 Laboratory diagnosis of HIV infection in nonbreastfed infants

The gold-standard test for HIV infection in infancy is HIV DNA PCR on peripheral blood lymphocytes [291], although some studies are now demonstrating equal/increased early sensitivity with amplification of viral RNA [292]. As many infants are infected intrapartum and blood HIV levels may still be very low, HIV DNA is not amplified from all infected infants at birth. Indeed, a positive HIV DNA PCR result within 72 h of birth has previously been taken as evidence of intra-uterine transmission [293]. Within the first weeks of life the sensitivity of the test increases dramatically and by 3 months of age at least 95% of nonbreastfed HIV-infected infants will be detected. In view of the genomic diversity of HIV a maternal sample should always be amplified with the first infant sample to confirm that the primers used detect the maternal virus. If a maternal virus cannot be detected by the HIV DNA PCR used then a different primer set, or a different test (e.g. HIV RNA PCR/ Nucleic Acid Sequence Based Amplification (NASBA)/HIV culture), should be used [294,295].

It is recommended to test infants at 1 day, 6 weeks, and 12 weeks of age. If all these tests are negative and the baby is not being breastfed, then parents can be informed that the child is not HIV infected. Evidence from the French

perinatal cohort demonstrated that neonatal ART, especially if more than one drug, can delay the detection of both HIV DNA and RNA in the infant [296]. For this reason, the second HIV DNA PCR is collected at 6 weeks of age, after 2 weeks off PEP.

For infants at high risk of infection an additional early HIV-DNA PCR may be undertaken at 2–3 weeks of age. If this is found to be positive this investigation should be immediately repeated on a further sample to ensure rapid confirmation of the diagnosis and to enable the establishment of combination antiretroviral treatment to try to avoid the development of HIV encephalopathy.

Loss of maternal antibodies is subsequently confirmed at 18 months of age. Ideally an HIV antibody test should be used to confirm loss of maternal antibodies rather than a combined HIV antibody/antigen test. The newer combined tests are highly sensitive and may give a positive HIV result until up to 2 years of age [297].

If an infant is found to be HIV infected after perinatal ART exposure then the mother and infant should have urgent HIV resistance testing to delineate the reasons for treatment failure and to help guide further treatment.

16.7 A managed network for children with HIV in the UK

Where an infant is found to be HIV infected, an urgent referral to the local specialist clinic should be made so that early combination ART can be started. HIV services for children in the UK are now organized in managed networks [Children's HIV National Network (CHINN)]. The details of the CHIN Network and contact details for local paediatricians can be found in the CHINN report at www.chiva.org/ [298].

16.8 Prophylaxis, immunizations and clinical monitoring

Primary PCP in infants with HIV remains a disease with a high mortality and morbidity [299]. However, as the risk of neonatal HIV infection has fallen to <1% where mothers have taken up interventions, the necessity for PCP prophylaxis has declined and in most European countries it is no longer prescribed routinely. However, co-trimoxazole as PCP prophylaxis should still be prescribed for infants born to mothers at high risk of transmission (see Table 5 for dose).

For infants born to HIV-infected mothers, the routine primary immunization schedule should be followed at 2, 3 and 4 months, except that Bacille Calmette-Guérin (BCG) vaccine should not be given until the infant is confirmed uninfected, with two negative HIV DNA PCRs off ART (see Section 10 for further information on HBV).

Considering the importance of confidentiality, where possible families should be strongly encouraged to inform

primary health carers, including midwives, health visitors and family doctors, about maternal HIV and indeterminate infants. This will enable the local team to give appropriate support and advice, especially regarding infant feeding and where the infant or mother is unwell.

16.9 Child protection

Rarely, pregnant mothers refuse treatment for their own HIV as well as interventions to reduce the risk of transmission to their unborn infant. Whether for social, religious or other reasons, mothers who have been reluctant to accept interventions may be able to do so where each aspect of the intervention package is dealt with separately (maternal ART, delivery, infant ART and infant feeding). This step-by-step approach has helped women to gradually make difficult personal changes to their birth plans. The input of the MDT is crucial to support these women as they are often the most isolated and unsupported.

Despite all efforts, where the MDT is unable to influence a mother's views antenatally, then a pre-birth planning meeting with social services should be held. The mother should be informed that it is the paediatrician's role to advocate on behalf of the child's well-being and therefore to prevent, where possible, HIV infection. If the mother continues to refuse any intervention package, then legal permission should be sought at birth to treat the infant for 4 weeks with combination PEP and in addition breastfeeding should be strongly discouraged. Preparation of the legal case may be lengthy and time-consuming; useful documentation can be obtained from colleagues who have already undertaken this.

16.10 Reporting and long-term follow-up

It is the responsibility of clinicians caring for women with HIV and their children to report them prospectively to the National Study of HIV in Pregnancy and Childhood (NSHPC). Reports should also be made to the International Drug Registry antenatally. See instructions below.

16.10.1 National Study of HIV in Pregnancy and Childhood (NSHPC)

This is the UK and Ireland surveillance system for obstetric and paediatric HIV, based at the Institute of Child Health, London. Diagnosed pregnant women are reported prospectively through a parallel reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists. HIV-infected children and children born to HIV-infected women are reported through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health. In the case of some units

Table 6 Classification of levels of evidence and grades of recommendations

Classification of evidence levels	
Ia	Evidence obtained from meta-analysis of randomized clinical trials
Ib	Evidence obtained from at least one randomized clinical trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities
Classification of grades of recommendations	
A	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation (Evidence level I)
B	Requires the availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (Evidence levels II and III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (Evidence level IV)

with large caseloads reporting is direct to the NSHPC. For further information, see the NSHPC website or e-mail nshpc@ich.ucl.ac.uk.

Website: www.ucl.ac.uk/paediatric-epidemiology/nsh/nshpc.html.

16.11 Antiretroviral Pregnancy Registry

Research Park, 1011 Ashes Drive, Wilmington, NC 28405, USA

In UK: Tel: 0800 5913 1359; fax: 0800 5812 1658

For forms visit: www.apregistry.com.

17.0 Infant feeding and HIV transmission during breastfeeding

World-wide, breastfeeding is an important route of HIV transmission from mother to child. In the UK, where safe infant feeding alternatives are available and free for women in need, HIV-infected women are advised not to breastfeed their infants. Postnatally, mothers should be advised that, although ART is likely to reduce free virus in the plasma and cell-associated virus in breast milk, the presence of HIV-1 DNA remains unaffected and may therefore constitute a transmission risk [300].

17.1 Risk of HIV transmission via breastfeeding

The only randomized clinical trial of breast *vs.* formula feeding to date was undertaken in Nairobi and confirmed the substantial risk of transmission through breastfeeding [301]. HIV-infected pregnant women, none of whom had received antiretroviral prophylaxis during pregnancy, were allocated to either breast ($n = 212$) or formula ($n = 213$) feeding, and the median duration of breastfeeding was 17 months. Adherence to assigned feeding modality was 96% in the breastfeeding arm and 70% in the formula arm. The cumulative probability of HIV infection at 2 years of age

was 36.7% in breastfed infants and 20.5% in formula-fed infants. The estimated absolute rate of transmission through breastfeeding over 2 years was 16.2%, doubling the overall rate of transmission to 39% at 2 years of age.

The cumulative rates of transmission through breastfeeding observed in PMTCT trials are in line with the results from the randomized trial, with a 10–14% increase in breastfed infants infected between 4–6 weeks and 18–24 months of age [124,125,302–304]. In a recent meta-analysis, including data from more than 4300 children enrolled in randomized controlled trials of peripartum interventions in sub-Saharan Africa, early transmission was defined by a positive HIV test before 4 weeks, and late postnatal transmission (LPT) by a negative diagnostic test at, or after, 4 weeks of age, followed by a subsequent positive test result. The overall rate of transmission was 24% and, of the 993 infected children, the timing of acquisition was early in 314 (31.4%), late in 225 (23.1%) and unknown in 454 (45.4%). The mean duration of breastfeeding was nearly 7 months, and the median 4 months. There was a continued risk of transmission throughout the breastfeeding period, which was approximately constant over time. The cumulative probability of acquiring HIV infection after 4 weeks of age was 1.6% at 3 months, 4.2% at 6 months, 7.0% at 12 months and 9.3% (95% CI 3.8–14.8) at 18 months [305].

17.2 Factors associated with breastfeeding transmission of HIV-1

RNA viral load in milk is generally lower than in plasma, and frequently below the detection limit of current assays. In a study in South Africa [306,307], RNA viral load was quantified three times in the first 3 months after delivery, in samples taken from both left and right breasts from 145 lactating women. RNA shedding varied between breasts and over time [306]. Milk viral load was below the limit of detection of the HIV RNA PCR assay (<200 copies/

mL) in a substantial proportion of samples. Low maternal CD4 cell count (<200/ μ L) during pregnancy and raised sodium:potassium ratio (a marker of subclinical mastitis) were significantly associated with increased milk RNA viral load at all times [307]. Thus women with more advanced HIV are more at risk of breast-milk transmission.

Many women with HIV in the UK would prefer to breastfeed their infants if it was safe to do so. Results of randomized controlled trials of breastfeeding in mothers on combination ART, currently underway in a number of African countries, are thus awaited with interest. In the meantime exclusive formula feeding remains the recommended method for infant feeding in the UK.

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Table A1 Clinical scenarios

Scenario	Viral load at presentation	Antepartum antiretroviral	Viral load at 36/40	Mode of delivery and intrapartum antiretrovirals	Postpartum to child	Postpartum to mother	Level of evidence and grade of recommendation
1a	Mother does not need HAART according to BHIVA Guidelines <32/40 gestation	<10 000 copies/mL	Unlikely to be <50 copies/mL	PLCS at 38 weeks + i.v. ZDV	ZDV for 4 weeks	Stop	Ib A
1b	Treatment Naive	ZDV monotherapy starting 20–32/40	<50 copies/mL	PLCS at 39 weeks or SVD Oral HAART	ZDV for 4 weeks	Stop	III B
		or START (PI-based) commencing 20–32/40	>50 copies/mL	See Scenario 4	See Scenario 4	Stop ideally when viral load undetectable	IV C
2	Any	START (PI-based) commencing between 20–32/40	<50 copies/mL	PLCS at 39 weeks or SVD Oral HAART	ZDV for 4 weeks	Stop	III B
		HAART after 1st trimester	>50 copies/mL	See Scenario 4	See Scenario 4	Stop ideally when viral load undetectable	IV C
3a	Mother presents on HAART	Continue	<50 copies/mL	PLCS at 39 weeks or SVD Oral HAART	ZDV for 4 weeks (or other monotherapy component of HAART regimen)	Continue	III B
		Genotype and change to best option (expert advice)	>50 copies/mL	See Scenario 4	See Scenario 4	Continue	IV C
3b	Mother presents on HAART	Continue	50 copies/mL	PLCS at 39 weeks or SVD Oral HAART	ZDV or other monotherapy component of mother's HAART for 4/52	Continue	III B
		Genotype and change to best option (expert advice)	>50 copies/mL	See Scenario 4	See Scenario 4	Reassess	IV C
4	On HAART or START + viral load > 50 copies/mL at 36/40	Genotype and change to best option if possible (expert advice)	> 50 copies/mL	PLCS 38/40 + i.v. ZDV if no ZDV resistance on most recent genotype Consider additional sdNVP	Combination PEP	If on START – discontinue (cover NVP tail) If on HAART – continue	IV C
		Commence HAART	<50 copies/mL	See Scenario 2	ZDV 4/52	If baseline CD4 cell count suggests mother needs HAART – continue	IV C
5	Late presentation before onset of labour > 32/40	Commence HAART	>50 copies/mL or no result	PLCS at 38/40 + oral HAART + i.v. ZDV Consider sdNVP	Combination PEP		

Table A1. (Contd.)

Scenario	Viral load at presentation	Antepartum antiretroviral	Viral load at 36/40	Mode of delivery and intrapartum antiretrovirals	Postpartum to child	Postpartum to mother	Level of evidence and grade of recommendation
6	Threatened pre-term delivery and/or pre-term ROM			Vaginal swab for bacteriology and start two doses i.m. steroids 24 hours apart if <34 weeks			IV C
6a	Mother drug-naïve	Any		Consider Emg CS weighing up gestational age with viral load for 6a, 6b and 6c	Combination PEP but seek expert advice	If baseline CD4 cell count suggests mother needs HAART – continue	IV C
6b	Mother on HAART	> 50 copies/mL		As 6a Add i.v. ZDV where viral load is >50 copies/mL	Combination PEP Seek expert advice	Continue HAART but ensure cover NNRTI	IV C
6c	Mother on HAART	< 50 copies/mL		As 6a	(Monotherapy component of mother's regimen) for 4 weeks		IV C
7	Term pre-labour rupture of membranes						
7a	Mother not on HAART	Any		Caesarean ASAP (but not less than 2 hours after NVP) Give NVP then set up i.v. ZDV	Combination PEP Seek expert advice	Review maternal CD4 cell count and continue if needed Cover NVP tail if stopping	IV C
7b	Mother on HAART	> 50 copies/mL		As 7a	Combination PEP Seek expert advice	Optimize maternal HAART	IV C
7c	Mother on HAART	< 50 copies/mL		Induce vaginal delivery or Caesarean ASAP	Monotherapy for 4 weeks	Continue	IV C
8	Mother diagnosed after delivery	Any		N/A	Combination PEP for 4 weeks	Manage as nonpregnant	IV C
9	Presentation in labour HIV status unknown Point of care HIV test Unconfirmed HIV-positive Treatment naïve	Unknown		Active management of labour Emergency Caesarean 2 hours post sdNVP if not about to deliver	Combination PEP for 4 weeks	As per BHIVA Guidelines for established infection if mother HIV positive Cover NNRTI stop if CD4 count > 250 cells/μL	IV C

BHIVA, British HIV Association; HAART, highly active antiretroviral therapy; i.m., intramuscular; i.v., intravenous; N/A, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PEP, post-exposure prophylaxis; PI, protease inhibitor; PLCS, pre-labour Caesarean section; ROM, rupture of membranes; sdNVP, single-dose nevirapine; START, short-term antiretroviral therapy; SVD, spontaneous vaginal delivery; ZDV, zidovudine.